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ETIOLOGY AND SYMPTOMS OF NEUROCIRCULATORY ASTHENIA

ANALYSIS OF ONE HUNDRED CASES, WITH COMMENTS ON PROGNOSIS AND TREATMENT

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The term "neurocirculatory asthenia," adopted in America during the World War, and synonymous with the less satisfactory British expression "effort syndrome," was applied in an attempt to classify a large number of persons having symptoms referable to the cardiovascular system not dependent on any known pathologic process of the heart or blood vessels but often associated with a functional nervous disturbance. These symptoms were chiefly palpitation, shortness of breath, precordial pain or discomfort and exhaustion. One or more associated symptoms were often present: faintness, syncope, headache, dizziness, insomnia, increased perspiration, difficulty in swallowing, tremor, flushing and pallor. The borderline between the normal and the abnormal is ill defined, but neurocirculatory asthenia may be said to be present when the symptoms appear during such customary physical activities and excitements of daily life as previously caused no symptoms or which in the average person produce no symptoms.

Neurocirculatory asthenia is of great importance because of its frequency, because of the marked suffering and even invalidism that it may cause and especially because of the need for its proper recognition and early treatment. There has been much confusion concerning this syndrome; it is to be distinguished from irritability of the heart alone shown by premature beats or paroxysmal tachycardia. It is also to be distinguished from psychoneurosis as such, in which anxiety, hypochondriasis or hysteria is predominant. However, many of the persons of the neurocirculatory asthenic group are definitely neurotic or psychoneurotic, as noted by Rothschild [1] and others. Neurocirculatory asthenia is a much better term than effort syndrome, since the latter may be produced in normal people. The symptoms comprising effort syndrome in normal people are not exactly the same, as a rule, as the symptoms found in neurocirculatory asthenia; for example, precordial

1. Rothschild, M. A.: Neurocirculatory Asthenia, Bull. New York Acad. Med. **6**:223, 1930.

aching is more commonly found in the latter syndrome, while breathlessness is almost the universal complaint in the effort syndrome of normal people. The early designation "disordered action of the heart" of the British included cases of organic heart disease; furthermore, in the purely functional cases, such a term focused the patient's attention on his heart, a practice which is to be discouraged.

To throw more light on the subject of neurocirculatory asthenia we have analyzed the etiologic relationships and symptoms of patients seen by us in civilian life, particularly of 100 persons in hospitals and private practice encountered during the past few years: 50 patients without heart disease and 50 patients with heart disease.

LITERATURE

Hippocrates recognized that palpitation might result from emotion or excitement. Galen devoted part of his sixteen books on the pulse to the influence of the various emotions on the heart. Corvisart [2] in 1806 recognized that palpitation might be a symptom of no danger. In 1870 Austin Flint [3] wrote that "persons who make complaint of symptoms referable to the heart may suffer from a functional disorder only." Neurocirculatory asthenia includes most of the cases described in 1871 by Da Costa [4] as "irritable heart" and those of "disordered action of the heart" and "effort syndrome" of the British [5] during the World War (1914-1918). Other names, such as "vasomotor neurosis" and "soldier's heart" have also been used as designations of this condition.

As noted by Rothschild,[1] Brooks [6] and others, the medical profession did not appreciate the importance and frequency of this syndrome before the war of 1914-1918, in spite of the rather extensive literature on the subject, and even today (1933) it is but little recognized by many physicians. Most articles have dealt with the presence of this condition in soldiers, but it is also a common occurrence in civilian life.

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2. Corvisart, J. N.: Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux, ed. 1, Paris, Migneret, 1806.

3. Flint, A.: Functional Disorder of the Heart, A Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart, Philadelphia, Blanchard & Lea, 1859, p. 403.

4. Da Costa, J. M.: On Irritable Heart, Am. J. M. Sc. **61**:2, 1871.

5. Lewis, T.: The Soldier's Heart and the Effort Syndrome, New York, Paul B. Hoeber, Inc., 1919.

6. Brooks, H.: Syncope in Neurocirculatory Asthenia, Tr. A. Am. Physicians **39**:419, 1924; Neurocirculatory Asthenia, M. Clin. North America **2**:477, 1918; Functional Disturbances of the Heart, Philadelphia, J. B. Lippincott Company, 1932.

Of a series of 3,000 patients with cardiac symptoms or signs who sought medical advice, both in hospitals and in private practice in recent years in New England (White and Jones, 1928 [7]), 302, or 10 per cent, were found to have neurocirculatory asthenia alone and 62, or 2 per cent, were found to have neurocirculatory asthenia complicating organic heart disease; nearly 3 per cent of the 2,315 cases of organic heart disease showed well marked neurocirculatory asthenia.

PRESENT STUDY

In the series of 100 cases presented here group I consists of 50 cases of pure neurocirculatory asthenia, having no heart disease demon-

TABLE 1.—*Symptoms in Neurocirculatory Asthenia*

	Group I (50 Cases) Without Organic Heart Disease		Group II (50 Cases) With Organic Heart Disease		Total per Cent of 100 Cases
	Number Cases Having	Per Cent of Group	Number Cases Having	Per Cent of Group	
Palpitation	40	80	38	76	78
Respiratory discomfort	39	78	38	76	77
Precordial pains or aches	32	64	42	84	74
(with radiation of pain)	16	32	17	34	33
Exhaustion or easy fatigability	34	68	39	78	73
Functional gastro-intestinal symptoms	20	40	24	48	44
Faintness	18	36	20	40	38
Syncope	10	20	9	18	19
Headache	15	30	22	44	37
Dizziness	16	32	21	42	37
Insomnia	9	18	21	42	30
Increased perspiration	10	20	8	16	18
Tremor	9	18	4	8	13
Flushing	5	10	5	10	10
Pallor	7	14	1	2	8
Precordial tenderness	11	22	6	12	17
Globus hystericus	4	8	7	14	11

strable by physical, electrocardiographic and roentgen examination, while group II consists of 50 patients with organic heart disease complicated by neurocirculatory asthenia. Twenty-five patients with "neurasthenia," group III, and a like number with psychoneurosis, group IV, have also been studied with particular reference to the frequency of occurrence of the cardinal symptoms of neurocirculatory asthenia when this syndrome as such did not exist in the latter groups. The borderline between neurasthenia and neurocirculatory asthenia is very vague, and certain of the cardinal symptoms of neurocirculatory asthenia may occur in the patients of the former group when the chief complaint is not referable to the cardiovascular system. In groups III and IV all

7. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, Am. Heart J. **3**:302, 1928. White, P. D.: Cardiac Neuroses, in Nelson Loose Leaf Medicine, New York, T. Nelson & Sons, 1920, vol. 4, p. 635; 1931 edition, vol. 4, p. 447; An Important Consideration in the Analysis and Management of Heart Trouble: 4 Cases, New England J. Med. **199**:148, 1928.

patients were excluded whose chief complaints were related to the cardiovascular system or whose conditions were diagnosed as neurocirculatory asthenia, effort syndrome or cardiac neurosis.

ETIOLOGIC DATA

Age.—The average age in these civilian cases was higher than that among soldiers during the war, doubtless because we are dealing with all ages in the community. The fact that young people in civilian life are ordinarily not subject to as much strain as soldiers during war is probably another factor of significance. The ages at the onset of symptoms in our group of 100 cases ranged from 12 to 69 years, with the average age 35¾ years (31½ years in pure neurocirculatory asthenia and 40 years for the group with complicating organic heart disease). There were 9 patients in the second decade, 25 in the third, 34 in the fourth, 21 in the fifth, 6 in the sixth and 5 in the seventh.

TABLE 2.—*Symptoms in Neurocirculatory Asthenia*

	Group III (Neurasthenia, 25 Cases)		Group IV (Psychoneurosis, 25 Cases)		Total per Cent of 50 Cases
	Number Cases Having	Per Cent of Group	Number Cases Having	Per Cent of Group	
Palpitation	12	48	9	36	42
Respiratory discomfort	9	36	8	32	34
Precordial pains or aches	8	32	7	28	30
Exhaustion	10	40	4	16	28

It is of interest that Lincoln [8] reported five instances of what she described as effort syndrome in children from 4 to 9 years of age, the group consisting of 3 boys and 2 girls; such early incidence is rare.

Sex.—The females outnumbered the males, 69 to 31, the percentage of females being slightly higher in group I than in group II (37 to 32). Twenty-two of the patients were unmarried (15 per cent of group I, 7 per cent of group II). Sexual irregularities or unhappy marriages played an important rôle in initiating symptoms in 4 patients of group I and in 1 patient of group II.

Constitutional Type.—As to the type of build most often affected, only 9 per cent of the patients were poorly developed or undernourished, while the majority, 81 per cent, were well developed and well nourished or obese (18 per cent); the remaining 10 per cent fell between these extremes. It is the common belief that the person of asthenic build is the most common type; we did not find this to be true.

Ninety-eight of our 100 patients were white and 2 were Negroes.

8. Lincoln, E. M.: The Hearts of Normal Children, Am. J. Dis. Child. **35**: 398 (March) 1928.

Occupation.—People engaged in almost all occupations were represented among our patients, housewives, trained nurses, teachers, clerks, students and doctors comprising the greater percentage, with the housewives predominating (51 per cent). Ninety-one per cent had sedentary occupations while only 9 per cent performed laborious tasks.

Causative Factors.—The factors initiating symptoms or contributing to them are numerous; in fact, in many cases it is difficult properly to evaluate these factors, especially when several factors seem to be playing a part. In the group in which there is a definite neurogenic element present (classification, p. 639), we encounter many people in whom symptoms of neurocirculatory asthenia develop on slight provocation, while in others the symptoms develop only after many trying experiences. The neurogenic element may vary from a mere state of anxiety to psychoneurosis, epilepsy or insanity. Four per cent of our patients had epileptiform seizures, while one patient was definitely paranoid. Oppenheimer and Rothschild [9] found a family history of epilepsy in 15 per cent and of insanity in 23 per cent of 100 cases of neurocirculatory asthenia studied by them, while in the same number of controls there was a negative history for both epilepsy and insanity. Boas [10] stated that "the anxiety neurosis, and the varied psychic disturbances that contribute so largely to the development of the picture of neurocirculatory asthenia may be regarded as producing excessive and exaggerated stimuli which reflexly affect the heart through the corticomedullary pathways, whose course is still unknown."

Such a factor as anxiety over family, finances or disease is often contributory. Sexual irregularities, such as maladjustment, overindulgence or an unhappy marriage, may be an evidence of the neurogenic element. In several of our patients with changes due to pregnancy or to the menopause, the physiologic processes were found to upset the delicate balance of persons previously considered normal and to initiate symptoms of neurocirculatory asthenia. It is apparent that these persons did not have the normal reserve, that something was lacking in their make-up. This lack of normal reserve varied greatly in different patients. The others (10 per cent) showed symptoms only on marked provocation, as persons who had worked hard for many years without a vacation or who had worked without sufficient daily rest.

Infectious diseases or operations are sometimes responsible for initiating symptoms of neurocirculatory asthenia; 9 per cent of our patients belonged to this group. Scarlet fever, pneumonia, infections

9. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, J. A. M. A. **70**:1919 (June 22) 1918.

10. Boas, E. P.: Neurogenic Disorders of the Heart, Am. J. M. Sc. **176**:789, 1928.

of the upper respiratory tract and arthritis were the infections noted in our patients. Grant,[11] Lewis [5] and others have observed that malaria, rheumatic fever and gastro-enteritis, as well as many other infectious or constitutional diseases, may be the initiating factors. We found that often there is an interplay of the infectious and neurogenic elements, as suggested by Gunewardene.[12] In support of this view, we have noted a few patients in whom symptoms have persisted for years after recovery from some infectious disease. The postinfectious group usually complains of exhaustion primarily and to a less extent of dizziness and palpitation; however, in those of dual origin precordial pain and shortness of breath may become prominent after a time.

We made observations concerning the use of coffee, tea, alcohol and tobacco in our group. It was found that 33 per cent of the 100 patients used no coffee or tea, and 79 per cent no tobacco, while 89 per cent abstained from alcohol; 56 per cent used moderation in respect to coffee, 37 per cent to tea, 11 per cent to tobacco, and 9 per cent to alcohol; this leaves only a small percentage that indulged excessively. Seldom did a patient use more than two of the aforementioned substances. It was not unusual for a patient to volunteer that he or she was sensitive to one or more of them, and a few patients had symptoms only after alcoholic sprees or excessive use of tobacco or coffee. This is in contrast to the habits of 100 controls of exactly the same sex and age distribution and of the same social status (50 of them with organic heart disease): 23 per cent used no coffee or tea, 62 per cent no tobacco and 69 per cent no alcohol. We conclude, therefore, that coffee, tea, alcohol and tobacco are not causes of neurocirculatory asthenia, although they may be aggravating factors, and that persons with or subject to neurocirculatory asthenia indulge in these things less than do other members of the community without neurocirculatory asthenia.

Nearly one half (44 per cent) of our patients suffered from some functional gastro-intestinal complaint, varying from occasional nausea, vomiting, or heart-burn to frequent episodes of severe abdominal distress, which in no case proved after careful study to be of organic origin. It has been noted before that many patients whose chief complaint is referable to the gastro-intestinal tract also complain of one or more of the cardinal symptoms of neurocirculatory asthenia.

Disease of the thyroid gland had occurred as a past event in 2 of the 100 patients, thyrotoxicosis in 1, in group I, and colloid adenoma in the other, in group II. The patient of group I was a woman

11. Grant, R. T.: Observations on the After Histories of Men Suffering from the Effort Syndrome, Heart **12**:121, 1925.

12 Gunewardene, H. O.: The Etiology of Effort Syndrome, Lancet **1**:885, 1920.

42 years old, who had had symptoms for a year, including: fleeting pains in the precordium radiating to the left arm, palpitation, shortness of breath (sighing), flushing, exhaustion, loss of weight and a slight increase of perspiration. She was operated on for the hyperthyroidism with a control of that factor; examination of the excised gland revealed primary hyperplasia; the basal metabolic rate, which had been plus 22 per cent before surgical intervention, dropped to minus 12 per cent after operation. However, when seen by us fifteen months after the operation she complained of attacks of fast pulse (probably paroxysmal tachycardia) and fleeting precordial pain radiating to the left axilla. She sighed frequently and was found to have no evidence of heart disease. The second patient was a woman 52 years old with hypertensive heart disease, chronic arthritis, colloid goiter and perhaps a slight hyperthyroidism (basal metabolic rate plus 20); she had had symptoms referable to the heart for two years. Two years after thyroidectomy the symptoms had abated very little. In both cases the neurocirculatory asthenia continued with little or no improvement after the disease of the thyroid gland had been eradicated. Of course, effort syndrome simulating neurocirculatory asthenia is the rule when thyrotoxicosis is present.

While neurotic and psychoneurotic patients may have neurocirculatory asthenia, it is also true that many of them have no symptoms referable to the cardiovascular system. In reviewing cases of neurasthenia and psychoneurosis, it was noted that in a number of them one or more of the cardinal symptoms of neurocirculatory asthenia was present, though these were not chief complaints and were elicited only on close inquiry.

It is our belief that usually in the histories of the patients with neurocirculatory asthenia possible neurotic or psychoneurotic factors are not sufficiently investigated. Rothschild and Oppenheimer [9] thought that psychoneurosis and the "irritable heart" of soldiers might result from a common but as yet unknown cause. They have suggested that such factors as enuresis, childhood frights, excessive absorption in religion and moodiness should be considered in the analysis and classification of neurocirculatory asthenia. We believe that definite neurogenic elements can be discovered in at least 75 or 80 per cent of these patients.

Based on the etiologic data studied, we suggest the following useful etiologic classification of neurocirculatory asthenia:

Type A:

(1) That which follows severe infection, operation, or other illness.

(2) That following prolonged, fatiguing work or strain of some other sort without respite.

Type B:

(1) That following a slight to moderate infection, operation or other illness.

(2) That following a moderate amount of fatiguing work or a strain of any sort.

Type C:

That occurring after little or no strain, but much aggravated by illness or fatigue.

A (1) and (2) may occur in people with normal constitutions, B (1) and (2) in the borderline group and C in those who are definitely inferior constitutionally. There may be combinations of A (1) and (2), A (1) and B (2), B (1) and (2), or B (1) and A (2).

According to this classification, 9 per cent of our patients belonged to group A (1) and 10 per cent to A (2), while 61 per cent belonged to group B and 20 per cent to group C.

SYMPTOMS AND SIGNS

We found that four symptoms, namely, palpitation, respiratory discomfort, precordial distress and exhaustion, occurred with almost the same frequency (from 73 to 78 per cent) in our 100 patients; they may be called the cardinal symptoms of neurocirculatory asthenia. Other symptoms which are often or sometimes noted are: faintness, syncope, insomnia, headache, dizziness, increased perspiration, difficulty in swallowing, tremor, flushing and pallor. These symptoms occur with almost the same frequency in patients with pure neurocirculatory asthenia as in those having an associated organic heart disease (table 1).

Palpitation was slightly more common in group I (80 per cent) than in group II (76 per cent) and usually consisted of the subjective sensation of pounding or of forceful beating of the heart at either a normal or a rapid rate. Occasionally a patient with pure neurocirculatory asthenia complained of irregular palpitation, but for the most part it was described as fast and regular. As expected, patients of group II complained more often of an irregular palpitation, since all of these patients had organic heart disease. Often palpitation only occurred after an emotional upset or after exercise. The pulse rate is often 150 or 160 or more after some slight stimulus and gradually returns to normal, usually requiring a much longer time to do this than in normal persons. Several of our patients with a pulse rate of from 80 to 90 during rest, experienced an acceleration to 140 to 160 simply through the excitement of having an electrocardiographic tracing made. A few patients were aware of palpitation only at night when in bed, especially when lying on the left side. Others were conscious of the heart beating most of the time, though it might be at a normal rate. Premature beats were infrequent in the cases of pure neurocirculatory

asthenia (once in 50 cases), but they may occur with regularity, even producing a bigeminal rhythm of the pulse. When bigeminy is present it usually disappears after exercise. It should be emphasized that the term "irritability of the heart" as used at the present time often refers to a normal heart having either auricular or ventricular premature beats. Frequently such patients are conscious of extrasystoles, but seldom do they suffer from neurocirculatory asthenia.

Respiratory discomfort or even actual dyspnea was the second most common symptom (77 per cent), and like palpitation it was more often subjective than objective, being an unpleasant consciousness of the ordinary respiratory act without much evident labor, distress or rapidity of respiration. Sometimes, however, there is tachypnea, and during the World War patients were noted with extreme but temporary acceleration of the respiratory rate, even to 100 or more per minute. The dyspnea may occur during rest, but more often it comes on after excitement or from slight to moderate exertion, depending to some extent on the degree of neurocirculatory asthenia. If the dyspnea occurs at rest, the patient when questioned usually answers that he or she feels as though not enough air were getting into the lungs and that therefore it is necessary to take a long breath, which is often evidenced by a deep, sighing inspiration. This is a useful sign in confirming the diagnosis of neurocirculatory asthenia. Sighing was recorded in 35 per cent of the cases of the present series; it was noted in 80 per cent of 100 cases reported by White and Hahn.[13] During rest in neurocirculatory asthenia the respiratory rate is usually normal or only slightly increased in rate, while after exercise it is often increased out of proportion to the amount of exertion and may be much shallower than normal. Often a patient will complain that he or she has had to give up some sport because of shortness of breath or exhaustion.

Precordial pain or discomfort occurred in 74 per cent of our patients, somewhat more commonly in those with organic heart disease (84 per cent in contrast to the 64 per cent of the patients without organic heart disease). It varies from an occasional "heartache," usually a constant dull aching or burning sensation, to the sharp needle-like or knifelike pain which lasts a few seconds, but which may recur over periods of minutes to hours. The location, character and duration of the pain or discomfort of neurocirculatory asthenia clearly distinguish it from angina pectoris. Radiation of the precordial discomfort of neurocirculatory asthenia to the left arm, axilla, shoulder,

13. White, P. D., and Hahn, R. G.: The Symptom of Sighing in Cardiovascular Diagnosis: With Spirographic Observations, Am. J. M. Sc. **177**:179, 1929.

scapula or even to the right arm may occur (as in 33 of 74 patients of our series; once to the neck and once to both arms). The more severe the discomfort, the more likely the radiation. Usually the discomfort occurs over the apex or lateral wall of the chest, but it may involve the whole left side of the chest. Not infrequently women complain of soreness or pain in or just under the left breast, which is not dependent on disease of the breast, but is evidence of the discomfort just described. Precordial tenderness not infrequently occurs in these patients and may also be present even when there is no precordial discomfort (1 of 17 cases); when present either with or without precordial discomfort, it is an important confirmatory sign of neurocirculatory asthenia.[14a] The examiner should not inquire regarding precordial tenderness until he has closely observed the patient's facial expression during the palpation of the chest.

Exhaustion or easy fatigability occurred in 73 per cent of the 100 cases, occurring in varying degrees. It may be constant or intermittent, occurring only at the time of, or sometimes apparently initiating, an episode of neurocirculatory asthenia. Exertion or emotional strain seems to increase the ease of fatigability.

An attempt was made to determine the most frequent combination of symptoms. It was found that precordial distress, palpitation and shortness of breath occurred in 49 per cent of our patients, pain and palpitation without shortness of breath in another 11 per cent, pain and shortness of breath without palpitation in 10 per cent and pain alone in 4 per cent. Fifty-three of 74 patients (72 per cent) with pain also complained of exhaustion. In the group without pain other combinations of symptoms occurred: palpitation, shortness of breath and exhaustion (15 per cent), palpitation and exhaustion (2 per cent), shortness of breath and exhaustion (3 per cent) and palpitation and shortness of breath (2 per cent). In the remainder, various other combinations of the associated symptoms occurred.

Lewis [5] stated that syncope occurs not infrequently with "the effort syndrome" (neurocirculatory asthenia), while others believe that it occurs only rarely. It was noted in 19 per cent of our patients, but in them not often as a rule; in a few cases it happened frequently, even up to several times a week. Faintness is a much more frequent symptom than syncope; we found it in 38 of our group of 100 patients. It may occur after emotional strain or may be present only when the patient experiences some of the cardinal symptoms of neurocirculatory asthenia. It may or may not precede syncope. It is often accompanied

14a. Kellogg, F., and White, P. D.: The Clinical Significance of Precordial Tenderness—The Relationship of Such Tenderness to Pain, New England J. Med. **206**:659, 1932.

by dizziness. Culpin [14b] stated the belief that these attacks of faintness originated with anxiety and are primarily of emotional origin, being identical with the "nervous attacks" of the sufferer with an anxiety condition. He further stated that "there is no line to be drawn between these attacks and others, usually called hysterical, in which emotion finds expression in motor activity."

The symptom of increased perspiration occurred in 18 per cent of our cases, tremor in 13 per cent, flushing in 10 per cent and pallor in 8 per cent; these may be considered as confirmatory symptoms of neurocirculatory asthenia, but when existing alone they certainly are not diagnostic of it. Increased perspiration may be a troublesome complaint. Insomnia is rather frequent in neurocirculatory asthenia, having occurred in 30 per cent of our cases. Eleven patients complained of symptoms suggestive of globus hystericus, varying from a choking sensation when tired to a full sized globus.

Emphasis should be placed on the frequency with which functional gastro-intestinal symptoms accompany neurocirculatory asthenia; this happened in 44 per cent of our series. These gastro-intestinal symptoms vary from an occasional spell of nausea, vomiting or slight, shifting abdominal distress to frequent and severe symptoms.

In attempting to determine the most frequent "chief complaint" at the time of the patient's first visit to us, it was found that often there were several symptoms almost equally prominent in the same patient. The cardinal symptoms of neurocirculatory asthenia which occurred as chief complaints are: precordial pain or distress in 41 per cent of our patients (in addition, angina pectoris occurred six times in group II), shortness of breath in 35 per cent, palpitation in 34 per cent and exhaustion in 25 per cent.

In group II (patients with neurocirculatory asthenia and organic heart disease) the symptoms were essentially the same in character and quantity as in group I, the cardinal symptoms occurring with approximately the same frequency in each group, as noted in table 1. The greater frequency of precordial pain, aching or distress in group II can possibly be explained by a greater consciousness of the heart, due to the fact that 26 of 50 patients of this group had enlargement of the heart. In group II there were 14 cases of hypertensive heart disease, 14 cases of coronary disease, 1 case of syphilitic aortitis and 29 cases of rheumatic heart disease, with 15 of the last named group showing lesions of both the aortic and the mitral valve. Several of the 50 patients in group II showed combined etiologic factors; 3 of the patients with hypertension had evident coronary disease, 3 of those with

14b. Culpin, M.: The Psychological Aspects of the Effort Syndrome, Lancet **2**:184 (July 24) 1920.

rheumatic heart disease had coronary disease, and the 1 with syphilitic aortitis had coronary disease; hypertension occurred in 2 of the group with rheumatic heart disease. Seven patients suffered from angina pectoris, while 4 had either definite or suggestive histories of coronary thrombosis. Of the 29 patients with rheumatic heart disease, 17 gave definite histories of acute rheumatic fever and 1 other of chorea, while 11 gave no history of chorea or rheumatic fever; of these 11 patients, 2 had had scarlet fever, 3 frequent tonsillitis and 2 others pains in the joints or muscles without definite rheumatic fever. In 1 patient the neurocirculatory asthenia began several years before the attack of rheumatic fever, while in the others the rheumatic infection antedated the neurocirculatory asthenia by at least two years. Only 2 patients of group I had rheumatic fever.

It is important to realize that although a person may have definite organic heart disease, his or her symptoms may be, and often are, entirely on a functional basis not originating in the heart lesion. This happened in the case of a considerable proportion of the patients in group II, at least 70 per cent, while the symptoms of the remaining 30 per cent were also chiefly functional.

SIGNS

Size of the Heart.—A roentgenogram taken at a distance of 7 feet, a fluoroscopic examination or an orthodiagram was obtained of 41 of the 50 patients in group I, and in no instance was the heart enlarged, whereas a definite tendency toward a decreased cardiothoracic ratio was noticed in the poorly nourished patients as well as in several of those described as being well developed and nourished. Of the patients in group II, 14 had hearts of normal size, while 36 had from slight to moderate enlargement as shown by physical and roentgen examinations.

Murmurs.—Fifty per cent of group I had "functional" systolic murmurs, for the most part apical but often pulmonary, which were described as soft or faint. The murmurs were not increased after exercise and were usually lessened by deep inspiration.

Blood Pressure.—In group I the systolic blood pressure in 4 of 49 instances was above 150 mm. of mercury on the first examination, while subsequent readings for the same patients showed the pressure to be much lower. The same variation was found to be true for the diastolic pressures. In our group the blood pressures closely approximated those of normal persons of the same age and weight. The average pressure for group I was 129 mm. of mercury systolic and 78 mm. diastolic. It was noted that the systolic pressure of several patients in this group was more easily influenced by excitement and exertion than that of normal persons. The blood pressure in patients

of group II corresponded closely to that of other patients with the same types of heart disease.

Electrocardiograms.—One or more electrocardiograms were made of 35 patients of group I. Fifteen of these patients with pure neurocirculatory asthenia had sino-auricular tachycardia ranging in rate from 110 to 160, while one had premature auricular beats producing a bigeminy which reverted to normal rhythm after exercise. Eight patients had diphasic T waves in lead 2 with inverted T waves in lead 3. six obese patients had slight left axis deviation and 5 well developed and well nourished patients had a tendency to right axis deviation. Five patients gave histories of paroxysmal tachycardia. Electrocardiograms taken on one or more occasions of 42 patients of group II showed the usual changes expected for the particular organic heart disease present.

PROGNOSIS

Prognosis in uncomplicated neurocirculatory asthenia is always good so far as length of life is concerned. There is, however, some degree of incapacity, the amount depending on several factors: the severity of the symptoms, the constitutional make-up of the patient and the intensity or adequacy of the treatment. It should be borne in mind that with a return of the causative factors, there will probably be a return of the symptoms, especially in the cases of classes B and C. In the cases of group A, the symptoms often cease permanently after an adequate rest or convalescence.

A group of 601 patients with effort syndrome was studied over a period of five years by Grant [11] in 1925 to determine immediate prognosis of the condition. Of these, 15.3 per cent recovered entirely, 17.8 per cent improved, 56.2 per cent remained stationary and only 2 per cent became worse. The incidence of serious disease in this group was 8.7 per cent; the most frequent infection was tuberculosis (3.7 per cent). Definite heart disease developed in only 1 per cent. As noted by one of us (White, 1931 [15]), there is a distinct tendency for persons with neurocirculatory asthenia to live partially crippled lives.

TREATMENT

The most essential point in the treatment of neurocirculatory asthenia is to take the patient wholly into one's confidence, to explain carefully the nature of the condition, to dispel all fears of heart disease or, if any disease is present, to explain the degree of limitation of activity necessary in view of the organic disease and also to explain that the symptoms are dependent on the neurocirculatory asthenia and not on the heart disease.

15. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

The plan of life of the patients should be worked out with care and understanding. Each patient should realize that he or she must live within certain limitations, in order to avoid things that produce symptoms; these limitations vary in different persons. Usually normal but quiet work and play are advisable, with avoidance of late hours, coffee, tea, overindulgence in alcohol and tobacco, strenuous vacations, excitement in general, too many hours at work and undertaking new and burdensome tasks or duties. Often after a few follow-up visits over a period of a few months, the patient adjusts himself to his surroundings and has no further symptoms. In the more severe cases of groups B and C, either with a marked psychoneurosis or a definite constitutional defect, it may be wise to seek a consultation with a psychiatrist with the hope of clearing up emotional conflicts present. After this has been done it is wise to follow the patient from the cardiac point of view, giving helpful reassurance regarding the heart; psychoanalysis alone will not cure.

Numerous drugs have been tried in the treatment of neurocirculatory asthenia, but for the most part they have been found to be of little value except in very nervous patients for whom mild sedatives such as bromides or the phenobarbital derivatives are often helpful in the symptomatic treatment. Whether or not suprarenal sympathectomy may prove to be of value cannot as yet be stated; Crile [16] has reported good results in several cases.

Re-education and reassurance are the keynotes of treatment. For the more severe cases, however, saturation with rest at the beginning is often advisable, with the prescription of proper rations of rest thereafter. Suitable rationing of rest is to be recommended for all cases.

SUMMARY AND CONCLUSIONS

1. To throw more light on certain aspects of neurocirculatory asthenia (in particular, its etiology and symptoms) we have presented the analysis of 100 cases, 50 without and 50 with organic heart disease.

2. In this series of 100 cases the females outnumbered the males, 69 to 31.

3. The average age of civilian patients is higher than that among soldiers during the war, doubtless because one is dealing with all ages in the community. The ages in our series ranged from 12 to 69 years, the average age for 100 patients being 35¾ years (31½ years for those with pure neurocirculatory asthenia and 40 years for those with complicating organic heart disease).

16. Crile, G. W.: Recurrent Hyperthyroidism, Neurocirculatory Asthenia and Peptic Ulcer: Treatment by Operations on the Suprarenal Sympathetic System, J. A. M. A. **97**:1616 (Nov. 28) 1931; Denervation of the Adrenal Glands for Neurocirculatory Asthenia, Surg., Gynec. & Obst. **54**:294, 1932.

4. Only 9 per cent of our 100 patients were poorly developed or undernourished. The great majority were well developed and well nourished, or obese.

5. Neurocirculatory asthenia may be classified etiologically:

A (1) That which follows severe infection, operation or other illness (9 per cent of our cases). (2) That following prolonged fatiguing work or heavy strain of some other sort without respite (10 per cent of our cases).

B (1) That following a slight to moderate infection, operation or other illness (25 per cent of our cases). (2) That following a slight to moderate amount of fatiguing work or of strain of any sort (36 per cent of our cases).

C. That occurring after little or no strain, but tending to be much aggravated by illness or fatigue (20 per cent of our cases).

6. The borderline between the normal and the abnormal is ill defined, but it is best indicated by the appearance of symptoms in the course of the usual physical activities and excitements of daily life, which previously gave no symptoms, or which in the average person would produce no symptoms.

7. Neurocirculatory asthenia is to be distinguished from "irritability of the heart" alone as shown by premature beats or paroxysmal tachycardia.

8. It is also to be distinguished from neurosis as such, in which anxiety, hypochondriasis or hysteria is predominant. We have analyzed 25 such cases for comparison.

9. It differs from ordinary neurasthenia, in which the flight into disease is manifested primarily by lack of energy, easy mental and physical exhaustion and irritabilty. We have presented data with reference to symptoms in 25 cases of neurasthenia.

10. Neurocirculatory asthenia is a term to be preferred to effort syndrome in designating the condition under discussion, since effort syndrome may be produced in normal people.

11. Palpitation, respiratory discomfort, precordial pains or aches and exhaustion are the four cardinal symptoms of neurocirculatory asthenia. They occur in the order named with almost the same frequency (78 to 73 per cent of our 100 cases).

12. Radiation of the precordial discomfort of neurocirculatory asthenia to the left arm, axilla, shoulder or scapula may occur (in 33 of 74 cases of our own). The more severe the precordial discomfort, the more likely the radiation.

13. Sighing respiration and precordial tenderness are important confirmatory signs and are almost pathognomonic of neurocirculatory asthenia.

14. When neurocirculatory asthenia complicates organic heart disease the symptoms are essentially the same in character and quantity as they are in the absence of organic heart disease.

15. The fundamental mechanism of neurocirculatory asthenia remains obscure. Variations of the same mechanism in different persons or, indeed, even different mechanisms may give rise to the different combinations of symptoms and signs.

EXPERIMENTAL POSTOPERATIVE EDEMA

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In a previous communication [1] we discussed the occurrence of generalized edema of the tissues following ordinary surgical procedures. The edema described was observed in a series of thirty-four patients and was of varying degree, but at times amounted to anasarca. In certain instances it proved to be a serious postoperative complication, especially when occurring in the intestinal wall and parenchyma of the lungs. Death apparently resulted from the edema in one case, and it was believed that the swelling of the intestinal wall might have contributed definitely to the malfunctioning of a gastro-enterostomy in several instances. It was thought that the edema was fundamentally of the nutritional type frequently associated with a lowering of the serum protein. Such a lowering of the serum protein below the critical level actually was observed in nearly all the cases. In attempting to explain the occurrence of this interesting phenomenon it was obvious that frequently the associated undernutrition of long standing was of primary importance. It was also evident that other factors were operative which, if not equally important, were nearly as important as the state of actual undernutrition. It appeared, for instance, that in the absence of a considerable fluid intake the serum protein would not drop and the edema would not develop, even though undernutrition was present. In addition, we noted that the daily intake of sodium chloride by various routes was excessive in most of these patients; this was undoubtedly another important factor in the accumulation of fluid in the tissues. In one group of patients with perforated appendixes requiring drainage the element of undernutrition was absent, but the occurrence of generalized edema was no less striking than in others. The important factor appeared to be excessive drainage with con-

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1. Jones, C. M., and Eaton, F. B.: Postoperative Nutritional Edema, Arch. Surg. **27**:159 (July) 1933.

sequent loss of protein or the factor of sepsis, resulting in a generally increased permeability of the capillaries, or a combination of both.

It is our purpose to report the experimental production of postoperative edema. We have attempted to reproduce in animals the actual condition occurring in ordinary surgical procedures on human beings, particularly as related to abdominal surgery. In these experiments we have tried to control and study the effects of variations in diet, fluid intake, nitrogen intake, salt intake, operative shock, drainage and sepsis.

METHODS

Full grown male cats were used in these experiments, and all operative procedures were performed under full surgical anesthesia. The basic diet for normal cats contained 1 Gm. of nitrogen and 72 calories per kilogram of body weight with adequate mineral salts and vitamins. The diet contained the following, per kilogram of body weight:

Casein	2.5 Gm.
Hamburger steak	15.0 Gm.
Liver	6.0 Gm.
Cornstarch	3.0 Gm.
Sugar	3.0 Gm.
Butter	1.1 Gm.
Salt mixture	0.2 Gm.
Bone ash	0.4 Gm.
Harris yeast	0.1 Gm.
Cod liver oil	5 drops

Salt Mixture:	
Sodium chloride	10 Gm.
Calcium lactate	4 Gm.
Magnesium citrate	4 Gm.
Ferric citrate	1 Gm.
Compound solution of iodine	2 drops

The diets containing 0.5, 0.3 and 0.1 Gm. of nitrogen per kilogram of body weight were based on the standard diet with the casein, meat and liver reduced to the correct nitrogen content and the calories maintained by increased carbohydrate and butter content.

Before the cats were placed on the control diet a Ssabanajew-Franck gastrostomy was performed in most instances, so that if they refused to eat their quota of food they could be fed through the gastrostomy opening. The entero-anastomosis, when performed, was made between the upper portion of the jejunum and the lower part of the ileum. The cats were etherized, and the routine surgical technic used on patients was employed. In those experiments in which the production of serous drainage was attempted, a standard cigaret drain was placed in the peritoneal cavity under aseptic precautions. Sometimes the site of the drains became infected after ten days or two weeks, but usually after that length of time the omentum walled off the end of the drain, gradually forcing it out of the wound and causing drainage to cease. In only one cat did peritonitis result, but in several cats an abscess well walled off at the inner end of the drain was found at autopsy.

In producing abscesses the abdominal wall was shaved, and 1 cc. of turpentine was injected subcutaneously. Abscesses formed within three days and usually broke in five days with drainage of thick purulent material. As soon as one abscess started to heal another was produced, so that there was constant loss of drainage material.

Hypodermoclysis consisted of 5 per cent dextrose in water or physiologic solution of sodium chloride. The animals were given approximately the same amounts of fluid per kilogram of body weight as are administered frequently to patients during routine postoperative care.

The cats were kept in specially constructed individual cages so that the urine and stools could be collected separately without loss and be fairly accurately measured. The urine and stools were tested for the nitrogen content according to Kjeldahl's method. Urinary chlorides were determined by Folin's method. The serum protein, albumin and globulin were determined by the method reported by Howe;[2] the nonprotein nitrogen was determined by Folin's method and the serum chlorides by Fiske's method.

As soon as the cats were killed autopsy was performed. Sections of the heart, lungs, liver, pancreas, kidney, pylorus, midileum, ileum or anastomosis, abdominal wall and leg muscle were weighed immediately and dried to constant weight over a period of from five to seven days, and the percentage of water was calculated. Sections of these tissues were prepared for histologic examination. Each day before receiving the hypodermoclyses the cats were weighed and examined for any evidence of peripheral edema, and the output of urine and the sodium chloride content were measured.

In the protocols the results of the determinations are expressed as follows: serum protein and albumin in grams per hundred cubic centimeters; nonprotein nitrogen and sodium chloride of the blood and urine as milligrams per hundred cubic centimeters; the hemoglobin and hematocrit readings and the water content of the tissues in per cent.

EXPERIMENTAL RESULTS (CONTROL)

A group of control animals was studied in order to obtain figures for comparison with animals subjected to the several procedures. The animals were placed on a diet sufficient to maintain body weight, which contained 1 Gm. of nitrogen per kilogram of body weight and adequate minerals and vitamins for growth. Analyses of the blood (table 1) were made at the end of three weeks, at which time the animals were killed.

Specimens of the various organs were studied for water content as already described, and the results are given in table 2. These figures correspond fairly closely with those obtained by Skelton.[3]

As a further check on any possible changes that might occur because of variations in the diet alone, for a period of from three to four weeks the animals were placed on the basic diets except that the nitrogen content was 0.5, 0.3 and 0.1 Gm., respectively, per kilogram of body weight. Because there were no changes in the blood of any significance except for a lowered serum protein in cat 14, and because of the absence of any clinical edema, weights of tissues were not determined on any of these animals. Analyses of the blood of these cats at the end of the control period gave the values shown in table 3.

It is of interest that even under conditions of nitrogen deficiency there was no important drop in serum protein at the end of approximately one month.

2. Howe, P.: Determination of Proteins in Blood, J. Biol. Chem. **49**:109, 1921.

3. Skelton, H.: Storage of Water by Various Tissues of the Body, Arch. Int. Med. **40**:140 (Aug.) 1927.

TABLE 1.—*Blood Analyses in Control Animals*

Cat	Serum Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
42	7.1	4.1	3.0	34	658	85	40
43	8.8	5.3	3.5	32	658	80	41
44	6.9	4.1	2.8	30	650	80	39
45	6.3	4.9	1.4	26	660	80	45
46	7.6	4.7	2.9	30	672	80	38
29*	7.8	4.7	3.1	33	614	80	53
21*	7.0	...	...	42	640	90	38
31*	7.9	4.6	3.3	39	660	80	40

* No preliminary period on the weighed diet. The cat has been in the stock-pen on rations of raw meat and liver.

TABLE 2.—*Percentage of Water in Tissues in Normal Animals*

Cat	Heart	Lungs	Liver	Kidney	Pancreas	Pylorus	Mid-ileum	Ileum	Abdominal Wall	Leg Muscles
42	78.1	82.2	74.7	73.4	75.9	78.2	79.1	78.8	78.0	77.2
43	72.0	77.3	73.8	75.0	64.0	77.0	76.7	76.8	67.9	75.8
44	76.9	80.2	75.2	76.7	71.2	78.6	78.7	78.2	75.8	77.0
45	76.6	79.2	72.2	77.0	70.0	77.7	77.4	78.4	76.3	76.2
46	....	78.8	74.6	76.4	71.8	77.7	78.2	78.0	75.7	76.4
29*	75.3	77.0	75.8	78.4	69.8	75.7	73.7	74.1	72.3	75.7
21*	78.6	77.8	72.2	77.9	69.2	76.0	....	76.4	71.7	77.0
31*	73.0	76.1	73.8	73.6	70.0	75.6	76.6	75.5	72.3	74.5
26A*	73.9	79.2	75.0	78.0	73.2	81.4	....	77.5	71.8	75.4

* No preliminary period on the weighed diet. The cat has been in the stock-pen on rations of raw meat and liver.

TABLE 3.—*Blood Analyses in Control Animals on Nitrogen-Deficient Diet* *

Cat	Diet	Duration	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
12	0.5	Initial	5.0	6.8	3.1	33	678	80	38
		3 weeks	3.9	8.4	5.3	40	661	85	35
18	0.3	Initial	2.6						
		3 weeks	2.5	6.4	...	34	702	70	40
		5 weeks	2.6	7.1	3.2	31	690	70	38
13	0.1	Initial	2.5	6.3	3.4	37	658	80	33
		4 weeks	1.9	5.9	4.0	31	673	80	45
14	0.1	Initial	2.5	6.8	3.2	41	690	70	30
		4 weeks	1.9	5.1	3.1	35	702	70	35
27	0.1	4 weeks	2.8	6.9	3.8	31	702	70	35
22	0.1	Initial	2.2						
		3 weeks	1.6	6.8	3.5	24	672	60	24
		4 weeks	1.5	6.5	2.5	30	690	65	28
33	0.1	Initial	3.7						
		4 weeks	3.1	6.6	4.3	20	658	70	33
34	0.1	4 weeks	2.8	6.0	3.9	20	...	70	37
28	0.1	3 weeks	2.4	6.5	3.1	38	614	85	38

* Nitrogen content reduced to 0.5, 0.3 and 0.1 Gm.

I. EXPERIMENTAL RESULTS FOLLOWING HYPODERMOCLYSIS AND VARIATIONS IN DIET

The first group of experiments was carried out in an attempt to determine the effect of hypodermoclysis on the production of edema in animals which received diets respectively adequate and inadequate in nitrogen and in which hypodermoclysis constituted the only source of food. Determinations of the water content of the tissues were not made in all the animals receiving the diet and hypodermoclysis simultaneously. In animals receiving hypodermoclysis only, following a previously known diet, such determinations were made and are shown in the protocols. For several days preceding the period of the experimental weighed diet the animals received the diet of raw meat and liver given in the stock-pen, which contained more than 1 Gm. of nitrogen per kilogram of body weight.

Previous experiments [4] had already been carried out in an attempt to produce edema in animals with an inadequate nitrogen intake. In several instances these experiments included periods of from three to four months of marked nitrogen starvation and were associated frequently with transient drops in the serum protein and albumin to below the so-called critical level. In no instance did edema develop, and it was concluded that this was due to the fact that the animals were receiving relatively small amounts of fluid a day.

The protocols for the present experiments follow.

A. *Effect of Hypodermoclysis Accompanying the Maintenance Diet.*—Cat 57.—This animal was given the diet containing 1 Gm. of nitrogen and 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day for thirty-five days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
Initial	3.9	7.2	3.8	37	620	70	36
15	4.0	7.6	...	25	643	70	33
35	4.7	7.2	4.1	40	588	70	42

The cat thrived on the diet and was well and healthy at the end of the period. The output of urine was normal at all times.

B. *Effect of Hypodermoclysis in the Presence of an Inadequate Nitrogen Diet.*—Cat 56.—This animal was given the diet containing 0.1 Gm. of nitrogen and 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day for thirty-five days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
Initial	2.5	6.9	3.2	25	665	65	30
15	2.3	7.1	...	20	630	65	30
35	2.1	7.3	3.6	20	731	65	30

4. Unpublished data.

The cat was well and healthy at the end of the period. The output of urine was normal at all times.

C. *Effect of Hypodermoclysis Alone Following a Normal Diet.*—Cat 8.—This cat was taken from the stock-pens and given 100 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day. The animal lived only thirty-one days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.8	11.3	4.6	85	672	75	35	104	.....
3	3.6	7.5	4.1	46	690	70	34	83	.....
7	3.3	6.6	4.4	48	660	70	34	57	.....
15	3.0	6.7	4.0	38	660	60	36	60	716
22	2.6	5.8	2.9	27	707	70	33	85	1,079
25	Hypodermoclysis increased to 200 cc. daily								
30	2.3	9.9	4.8	39	602	60	22	110	1,463
31	Cat died							150	2,160

Autopsy revealed nothing abnormal. The cat was very emaciated. The water content of the tissues (per cent) was:[5] heart, *80;* lungs, 78.3; liver, 68.6; pylorus, *81.6;* pancreas, *79.*

It is of interest to note the sharp terminal rise in serum protein and serum albumin in the absence of urinary retention. Examination of the water content of the tissues indicated beginning edema in the heart, pylorus and pancreas.

D. *Effect of Hypodermoclysis Alone after a Previously Deficient Nitrogen Diet.*—Cat 33.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty days; then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in water were substituted for the food. After seventeen days the cat became so weak that it was killed. At that time the front paws, legs and chest were slightly edematous. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.1	6.6	4.3	20	658	70	33	...	...
5	2.6	6.3	4.0	26	599	75	30	190	38
11	2.5	6.6	3.9	41	672	60	20	185	111
17	2.4	6.0	3.6	42	544	60	26	100	40

Autopsy revealed the legs and chest to be edematous. The tissue between the skin and the abdominal wall was filled with bubbles of fluid, although there was no excess of fluid in the abdomen. The intestine was large and bluish silver. There was questionable edema of the colon. No fluid was found in the lungs. The heart was flabby, and the pericardium contained a bloody fluid, probably caused by a puncture of the heart to obtain blood. The water content of the tissues (per cent) was: heart, *80.6*; lungs, *80.6*; liver, *74.4*; kidney, *76.3*; pancreas, *81.5*; pylorus, 80.4; midileum, *79.7*; ileum, *80.4*; abdominal wall, 76.5; leg muscle, *78.*

The histologic report showed very slight edema of the submucosa of the ileum and moderate edema of the interstitial tissue of the pancreas. The leg muscle showed a very slight trace of edema. All other tissues were free from edema.

Cat 27.—This animal was given the diet containing 0.1 Gm. of nitrogen for twenty-one days; then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet. Edema of the paws occurred after

5. Figures of more than 0.5 per cent above the maximum normal control figures are italicized to indicate edema.

eleven days and then disappeared until the fifteenth day, after which it appeared only transiently. The animal was killed because of weakness twenty-three days after the hypodermoclyses were started. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.8	6.9	3.1	32	702	70	35	100	580
8	2.4	6.4	2.7	25	655	70	30	278	2,209
11	2.3	6.0	3.0	25	690	60	20	210	2,100
18	2.0	6.5	3.5	28	614	65	17	280	2,632
23	1.8	7.2	4.9	28	526	65	17	200	1,774

Autopsy revealed edema of the legs only. The intestines were enlarged and very moist, but there were no other abnormalities. The water content of the tissues (per cent) was: heart, 76.5; lungs, 79.3; liver, 75.1; kidney, *79.3*; pancreas, *78.4*; pylorus, 79.1; midileum, *79.4*; ileum, *79.2*; abdominal wall, 73.1; leg muscle, 76.8.

The histologic report showed questionable edema of the leg muscle. The lymphatics were slightly prominent in the pylorus, midileum and terminal ileum, but there was no definite edema.

The terminal rise in the values for serum protein and serum albumin in cats 8 and *27* should be noted. These were undoubtedly premortem phenomena such as have been noted frequently by earlier investigators toward the end of experiments with starvation and probably represent a rather rapid dissolution of the tissues.

II. EXPERIMENTAL RESULTS FOLLOWING HYPODERMOCLYSIS AND VARIATIONS IN DIET ASSOCIATED WITH ENTERO-ANASTOMOSIS

A second group of animals was studied with a view to determining the effect of hypodermoclysis when diets of varying nitrogen content are given immediately after an entero-anastomosis. A gastrostomy was performed long before the entero-anastomosis was done, and we were therefore able to vary the food intake at will. The entero-anastomosis was performed between the upper jejunum and terminal ileum, and had the double advantage of allowing us to make observations on animals with a recent intestinal operation and also of interfering with the proper absorption of food because of the short circuit performed on the bowel. With the exception of cat 5 the animals received food during the postoperative period, although, because of the nature of the operation, the actual amount absorbed was not known. In this respect the procedure differed from that in a gastro-intestinal operation on a human being when there is virtual starvation for days. The amounts of fluid given by hypodermoclysis varied between 24 and 66 cc. per kilogram of body weight, which corresponds to between 1.7 and 4.6 liters for a man weighing 70 Kg. At times these amounts were undoubtedly excessive for both fluid and sodium chloride. There is no doubt, however, that not infrequently equivalent amounts have been administered as a routine to dehydrated patients after operation. As

a control experiment four animals were studied for the effect of anastomosis alone without hypodermoclysis. They were followed for periods of a hundred and fifteen, forty, eighteen and fourteen days after the anastomosis was performed. Protocols for these are not given, as edema did not develop.

From the control experiments it is obvious that the prolonged period of undernutrition associated with anastomosis of the jejunum and ileum did not result in the appearance of edema. There was an apparent increase in water in the lung tissue in one animal, but this is the only possible exception, and we cannot offer an explanation for it. Although the diets were adequate in every respect, it is obvious that these animals failed to absorb their food properly, as evidenced by a constant loss of weight. The absence of peripheral edema or edema of the tissues probably can be explained by the fact that the fluid intake was relatively low and no extra salt was administered.

A. *Experiment Showing the Effect of Entero-Anastomosis Combined with an Adequate Diet and Hypodermoclysis.*—Cat 30.—This animal was given the diet containing 1 Gm. of nitrogen for twenty-five days prior to anastomosis and for twenty-three days afterward, at which time 200 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day was substituted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.4	8.1	4.7	36	614	70	41	..	.....
9	2.7	7.3	3.8	36	687	70	37	42	50
16	2.7	7.2	3.9	57	681	70	30	57	374
25	2.2	7.3	3.6	58	678	..	..	68	280
25	Hypodermoclysis started								
29	2.3	5.1	3.1	60	688	60	27	120	1,200

Autopsy revealed the chest and paws to be edematous. A watery and mucoid stool was passed just before the animal was killed. Between the skin and abdomen there was much fluid and in the abdomen a slight excess of fluid. The lungs contained over 1 cc. of pleural fluid, and there was a slightly bloody fluid in the pericardial sac, probably from a puncture of the heart to get blood. The anastomosis was in perfect condition. The water content of the tissues (per cent) was: heart, *82.5*; lungs, *84.1*; liver, 75.2; kidney, *82.5*; pancreas, *82.9*; pylorus, *82.5;* midileum, *85.1;* anastomosis, *83.6;* abdominal wall, *79.5;* leg muscle, *78.6.*

The histologic report revealed slight edema in the lungs, anastomosis, midileum and pylorus.

Subcutaneous edema was noted only on the day the animal was killed. It is of interest that the appearance of edema and a lowering of the serum protein and serum albumin followed closely to the subcutaneous administration of the salt solution. There was also a slight terminal urinary retention.

B. *Experiment Showing the Effect of Entero-Anastomosis Combined with the Diet Containing 0.5 Gm. of Nitrogen and Hypodermoclysis.*—Cat. 38.—This animal was given the diet containing 1 Gm. of nitrogen for seven days prior to

anastomosis and the diet containing 0.5 Gm. of nitrogen for three weeks after the anastomosis, when 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis was substituted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.4	6.3	4.4	37	687	80	33	32	288
7	2.0	5.7	3.5	36	672	60	23	30	396
13	1.8	5.8	3.0	46	626	79	25	18	105
20	1.6	5.9	3.0	46	725	60	27	0	0
24	Hypodermoclysis started								
26	1.6	5.1	2.5	46	627	..	..	40	520

Two days after hypodermoclysis was started, the cat was killed because of weakness. Autopsy revealed nothing abnormal. The water content of the tissues (per cent) was: heart, *80.1*; lungs, *80.1*; liver, *75.9*; kidney, *80.9*; pancreas, *79.1*; pylorus, 78.5; midileum, *84.4*; ileum, 77.2; abdominal wall, *79.4*; leg muscle, *78.5*.

The drop in serum protein and serum albumin and the oliguria corresponded in time with the results obtained in cat 30.

C. *Experiment Showing the Effect of an Entero-Anastomosis Combined with Hypodermoclysis Alone.*—Cat 5.—This animal was given the diet containing 1 Gm. of nitrogen for thirty days prior to anastomosis. After the operation it received 100 cc. of 5 per cent dextrose in saline solution by hypodermoclysis each day. The cat lived for twenty-nine days after the operation. Diarrhea was present for seven days preceding death. Edema of the front legs and face appeared two days before death and disappeared on the following day.

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	4.2	10.7	2.9	55	1,070	85	47	55	.....
3	3.8	6.9	3.1	46	681	70	37	75	.....
7	3.4	6.8	3.1	37	702	70	33	50	.....
12	3.0	5.9	2.5	24	673	65	30	80	.....
15	2.9	7.3	2.5	31	672	65	30	83	.....
19	2.7	6.8	3.6	26	674	60	28	75	.....
27	2.3	5.7	3.4	26	655	60	20	20	.....
30	2.1	6.5	2.0	34	707	60	20	93	1,012

At autopsy the skin was juicy, but no fluid was found in any cavity. The heart was flabby, and the lungs were pale. There was questionable edema of the pylorus.

The histologic report revealed slight edema of the abdominal wall, leg muscle, pylorus and midileum. Questionable edema was evident in the submucosa of the anastomosed area of the intestine. The pancreas showed edema of the interstitial tissue. The heart, lungs and liver were normal.

This cat can be compared with cat 8 of the preceding group with the exception of the operation performed at the beginning of the experiment. The cats were approximately the same weight and received the same amount of fluid by hypodermoclysis, without any food by gastrostomy. The operative procedure was apparently associated with a more rapid loss of weight and an earlier appearance of edema, as shown by the watery diarrhea. The obvious edema of the tissue was also greater in cat 5.

D.—*Experiment Showing the Effect of an Entero-Anastomosis Combined with a Nitrogen-Free Diet and Hypodermoclysis.*—Cat 6.—This animal was given the diet containing 1 Gm. of nitrogen for thirty-three days prior to anastomosis,

which was followed by an adequate caloric diet of carbohydrates alone and a daily hypodermoclysis of 100 cc. of 5 per cent dextrose in saline solution, which was increased to 200 cc. two days before death.

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.
Initial	4.0	6.9	4.0	48	637	80	43	82
4	3.6	8.4	3.2	52	690	55	18	67
8	3.3	5.5	2.8	37	667	55	18	112
11	3.1	6.3	3.4	32	672	60	25	70
15	3.0	5.7	3.1	38	672	60	25	70
24	2.8	5.5	4.5	26	655	60	23	70
30	2.4	4.7	3.1	30	643	55	20	240

The cat lived for thirty days after the anastomosis; death was due to intussusception of the intestine 2 inches into the anastomosis from the short-circuited loop. The tip of the intussuscepted loop was gangrenous. Evidently all food went through the anastomosis from the contracted lumen of the short-circuited loop. There was no fluid or edema in the abdomen or pleural cavity on gross inspection. The legs were edematous.

The histologic report revealed congestion in the lungs and liver and moderate edema in the leg muscle. The intestine near the anastomosis showed edema of the submucosa, and the pancreas showed acute and chronic pancreatitis.

This experiment showed the effect of increasing the amounts of fluid on lowering the serum protein and serum albumin. There was a sharp drop in both when the hypodermoclyses were increased from 100 to 200 cc. a day.

E. *Experiments Showing the Effect of an Entero-Anastomosis Followed by Hypodermoclyses Alone and Subsequent Administration of Food.*—Cat 11.—This animal was taken directly from the stock-pen. An anastomosis was performed, after which the cat received a daily hypodermoclysis of 150 cc. of 5 per cent dextrose in saline solution until the thirteenth day, when the diet containing 0.1 Gm. of nitrogen was added. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.2	6.0	...	30	661	70	35	...	.....
8	1.7	4.2	2.9	38	702	60	18	165	1,550
14	1.5	5.9	2.4	30	672	60	20	140	1,484
14	0.1 Gm. nitrogen diet started								
22	1.4	4.6	2.1	26	672	50	12	190	2,128
23	1.4	4.3	2.0	35	624	..	..	191	2,120

The cat was killed twenty-three days after anastomosis, when edema was noted. The legs were baggy and filled with fluid. The abdomen contained 1 cc. of fluid; the same amount was in the pleural cavity and there was questionable fluid in the pericardium. The lungs were very pale. The water content of the tissues (per cent) was: heart, *78.5;* lungs, *87.8;* liver, *75.5;* kidney, *80.1;* pancreas, *78.8*; pylorus, 80; anastomosis, *80.2*; leg muscle, *78.*

Cat. 15.—This animal was taken from the stock-pen and anastomosis was performed. It received 200 cc. of 5 per cent dextrose in saline solution by hypodermoclysis daily until the nineteenth day after the operation when the diet containing 1 Gm. of nitrogen was substituted. Nine days after the operation a stitch abscess developed which broke and drained. The cat did not eat the 1 Gm. nitrogen diet well, so after a few days the diet was changed to meat and liver. Rapid improvement followed. After thirteen days on this diet the cat was put

on the 1 Gm. nitrogen diet again, but it refused to eat and died after two days. The edema disappeared as soon as the hypodermoclyses were discontinued and the protein diet given. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.0	6.1	4.5	42	634	85	45	...	.....
3	...	6.0	4.3	36	640	70	35	300	2,460
6	2.6	5.8	4.0	33	585	70	30	185	1,646
9	2.3	5.1	3.1	25	655	..	..	190	2,164
14	2.2	5.6	3.1	18	702	70	36	224	2,295
	Edema								
20	2.0	4.9	2.7	26	660	60	30	100	1,160
	Hypodermoclysis was stopped; protein food was given; edema disappeared								
33	1.9	7.9	6.7	30	614	..	..	...	.....
37	1.7	8.4	4.6	112	526	65	22	...	.....

Autopsy revealed the heart and lungs to be normal. The abdomen contained 20 cc. of yellow fluid. The loop of the intestine which had been short-circuited was greatly distended and dark red, owing to a volvulus in its center caused by the mesentery of the anastomosis.

The ascitic fluid contained: total protein, 5.4 Gm.: albumin, 2.4 Gm., and non-protein nitrogen, 144 mg. The water content of the tissues (per cent) was: heart, 76.3; lungs, 76.6; liver, *76.3;* kidney, *78.7*; pancreas, *78.2*; pylorus, 76.5; anastomosis, 78.4; abdominal wall, 77.3; leg muscle, 77.3.

The addition of very small amounts of nitrogen toward the end of the experiments on cat 11 was insufficient to maintain the serum protein at a normal level. Relatively larger amounts of fluid and salt were employed than in preceding animals, and edema occurred a little earlier. In cat 15 the timely administration of a completely adequate diet high in protein caused the disappearance of edema and complete recovery. Death was due to a volvulus. The occurrence of edema in nineteen days may have been hastened by excessive amounts of fluid and salt and also by the presence of sepsis. It is of interest to note the rapid rise in the serum protein and serum albumin as soon as a proper diet was instituted.

III. EXPERIMENTAL RESULTS FOLLOWING DIETARY VARIATIONS, AN ABDOMINAL OPERATION AND THE ADDITION OF SEROUS DRAINAGE

A third group of animals was studied with a view to determining the result of the addition of serous drainage to the previous procedures. The experiments consisted of placing animals on diets of different nitrogen contents over variable periods of time, after which an entero-anastomosis was performed and a drain was placed in the abdomen under aseptic conditions. Hypodermoclyses were administered in the same manner as previously described, but no food was allowed after the entero-anastomosis except for cat 4. It was believed that the additional factor of serous drainage produced by the introduction of a standard cigaret drain in the abdominal cavity might tend to lower the serum protein more rapidly than in the previous experiments and would at least tend toward a more rapid formation of edema. In every instance aseptic precautions were fully carried out during the operation for the entero-anastomosis and for the subsequent insertion of the drain. It was found practically impossible, however, to prevent the development

of a local infection around the drain after an interval of two weeks. In each instance the drainage from the cigaret drain was clear serous fluid for a reasonable number of days. Attempts to measure or collect this fluid were unsatisfactory, but in several instances there was an appreciable amount. Toward the end of the experiment there was an infection around the base of the drain, but with one exception this was completely walled off from the rest of the peritoneal cavity. It did, however, contribute an area of sepsis, so that an additional factor complicated the picture before the cats were killed. Protocols are given in the following section.

A. *Experiments Showing the Effect of an Entero-Anastomosis and Drainage, Plus Hypodermoclysis After a Diet Containing 1 Gm. of Nitrogen.*—Cat 1.—This animal was given the diet containing 1 Gm. of nitrogen for fifty-seven days prior to anastomosis with insertion of a drain. After the operation 150 cc. of 5 per cent dextrose in saline solution by hypodermoclysis daily was substituted for the diet. Diarrhea was present constantly after the operation, and there was a profuse discharge from the drain. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.6	6.3	2.1	43	672	60	42	170	.....
3	...	...	...	..	...	..	..	90	540
6	2.9	5.6	2.5	41	690	70	30	140	1,148
9	...	4.0	1.3	63	631	..	25	140	1,148

The animal was killed on the ninth day. There was much clear serous fluid oozing from the drain, and the abdomen was filled with ascitic fluid. The intestine was from two to three times the normal size and was filled with a dark brown, watery material. The pleural cavity contained fluid. There was an abscess near the gastrostomy opening which was filled with thick creamy pus, but it was not connected with the abdomen. The ascitic fluid contained: total protein, 0.9 Gm.; albumin, 0.6 Gm.; nonprotein nitrogen, 60 mg., and chlorides, 702 mg. The abdominal wall and anastomosis were the only tissuse to show a suggestion of edema. The water content of the tissues (per cent) was: heart, *79.7;* lungs, 81.3; liver, *72.7*; kidney, *77.3*; pancreas, *79.6;* pylorus, 80.9; anastomosis, *84.1;* leg muscle, *79.1.*

Cat 10.—This animal was given the diet containing 1.0 Gm. of nitrogen for eight days prior to anastomosis with a drain. Daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet after the operation. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	4.3	6.7	4.6	45	660	85	48	84	663
3	...	4.5	3.2	43	660	..	..	...	.....
7	3.9	5.0	1.9	37	655	80	32	160	1,888
8	...	4.4	2.2	33	645	65	20	190	1,980

Autopsy revealed a partially walled off abscess around the inner end of the drain. The intestine was normal. Some ascitic fluid was noted. There was no fluid in the pericardial sac or pleural cavity. All the organs were normal in appearance, and the anastomosis was in good condition. The ascitic fluid con-

tained: total protein, 4.5 Gm.; nonprotein nitrogen, 183 mg. The water content of the tissues (per cent) was: heart, *80;* lungs, 80; liver, *76.5;* kidney, 75.5; pancreas, 68.1; pylorus, 75.4; abdominal wall, 65.3; leg muscle, 73.

The rapid drop in serum protein and serum albumin is to be noted, as well as the absence of urinary retention and edema. The high percentage of water in the area of anastomosis in cat 1 is of interest, and may represent local edema after the operative procedure or possibly an accumulation of fluid occurring after trauma and a lowering of the serum protein.

B. *Experiments on the Effect of an Entero-Anastomosis and Drainage with Hypodermoclysis After a Diet Containing 0.5 Gm. of Nitrogen.*—CAT 12.—This animal was given a diet containing 0.5 Gm. of nitrogen for twenty-one days prior to an anastomosis and insertion of a drain, followed by daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution for fifteen days. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	5.0	6.8	3.1	33	680	80	58	...	.....
Initial	3.9	8.4	5.3	40	661	85	55	47	256
4	3.7	5.8	3.5	35	660	70	40	80	1,056
7	3.6	5.8	2.7	40	672	70	40	230	2,550
11	3.4	5.4	3.4	40	672	70	27	74	1,410
14	3.2	5.5	3.1	26	702	60	25	223	2,750
15	...	6.4	4.0	36	600	..	..	275	2,842

The cat was killed on the fifteenth day. Autopsy showed everything normal except an abscess well walled off at the end of the drain. The water content of the tissues (per cent) was: heart, *79.2;* lungs, 77.5; liver, 69.4; kidney, 77.5; pancreas, *76.3;* pylorus, 80; anastomosis, 76.5; leg muscle, *77.8.* There was no evidence of edema.

In spite of free serous drainage and the administration of fairly large amounts of salt solution no edema developed even with a drop in the serum protein to the critical level. It is to be noted that there was no urinary retention.

CAT 4.—This animal was given the diet containing 1 Gm. of nitrogen for seventy-five days, and then the diet containing 0.5 Gm. of nitrogen for eighteen days prior to anastomosis with a drain. After the operation the diet containing 0.1 Gm. of nitrogen and a daily clysis of 200 cc. of 5 per cent dextrose in saline solution were given. There was profuse serous drainage from the abdomen. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	3.1	6.5	3.4	45	690	75	41	42	546
Initial	2.9	7.8	4.2	37	672	75	34	80	512
3	...	6.3	4.0	37	672	..	..	190	1,929
6	2.4	5.9	3.5	25	602	65	30	30	468
9	2.4	5.3	3.3	33	678	55	20	268	2,160

The animal was killed nine days after the anastomosis was done. Autopsy showed a slight amount of pus around the drain, which was well walled off by the omentum. About 2 cc. of clear serous fluid was found in the abdomen. The intestine was greatly enlarged and swollen; no fluid was found in the lungs or heart. The water content of the tissues (per cent) was: heart, *79*; lungs, 81.7; liver, 74.7; kidney, 76; pancreas, *87.1;* pylorus, *81.8;* midileum, *81.6;* anastomosis, *79.1;* abdominal wall, 77.5; leg muscle, 75.1.

Histologic examination showed no evidence of edema.

This experiment is similar to the preceding one, but here the relative amounts of salt solution were much greater than those administered to cat 12, and it is to be noted that the fluid content of the tissues was beginning to rise.

C. *Experiments on the Effect of an Entero-Anastomosis and Drainage with Hypodermoclysis After a Diet Containing 0.1 Gm. of Nitrogen.*—Cat 13.—This animal was given a diet containing 0.1 Gm. of nitrogen for thirty-one days prior to an anastomosis and insertion of a drain and daily hypodermoclyses of 150 cc. of 5 per cent dextrose in saline solution after the operation. On the second day after the operation the paws, chest and face became edematous. Practically no urine was excreted after the operation. The animal lived for three days and received 450 cc. of fluid. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	2.5	6.3	3.4	37	658	80	33	..	...
Initial	1.8	5.8	4.0	30	672	70	45	15	150
1	...	...	...	..	...	..	..	0	0
2	...	...	...	..	...	..	..	20	497
3	...	4.3	3.3	35	672	..	..	25	490

The animal was killed because it was practically dead. The face, paws, and chest were edematous. No fluid was seen in the abdomen, but there was a slight excess of fluid in the chest. The anastomosis was in good condition. The kidneys were purplish, but the other organs appeared to be normal. The water content of the tissues (per cent) was: heart, *80;* lungs, *92.2;* liver, *76;* kidney, *80;* pancreas, 73.2; pylorus, *83*; anastomosis, 77; abdominal wall, *82.3*; leg muscle, 67.1.

The tissues of the pylorus and pancreas showed the only evidence of edema, which was slight.

Cat 14.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty-one days prior to anastomosis with insertion of a drain and daily hypodermoclyses of 150 cc. of 5 per cent dextrose in saline solution following the operation. The cat lived for two days after the operation, during which time it excreted no urine. It received 300 cc. of fluid by hypodermoclysis. There was much drainage, and edema in the front legs was noted. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Control	2.5	6.8	3.2	40	690	70	30	..	...
Initial	1.9	5.1	3.1	35	702	70	38	25	215
2	...	5.8	Dead when blood was taken; no urine since operation						

Autopsy showed the front legs, chest and shoulders bulging with fluid. Three cubic centimeters of ascitic fluid and 2 cc. of pleural fluid were found. The bladder was contracted and contained no urine. In the ascitic fluid the total protein was 6.6 Gm. and the albumin 5 Gm. The pleural fluid contained: total protein, 2.1 Gm.; albumin, 1.3 Gm. The water content of the tissues (per cent) was heart, *80.4;* lungs, *84.6;* liver, 74.7; kidney, *81.6;* pancreas, 67.4; pylorus, 73.5; anastomosis, 73.5; abdominal wall, 75.7; leg muscle, 77.3. The only tissues to show evidence of edema were those of the abdominal wall and the pancreas.

In sharp contrast to the preceding experiments marked peripheral and fairly definite visceral edema occurred within from forty-eight to seventy-two hours after the operation. Drainage was profuse, and there was marked urinary retention of water and salt.

IV. EXPERIMENTS SHOWING THE EFFECTS OF PUS FORMATION ON THE PRODUCTION OF EDEMA

In the following group of animals it was decided to introduce the factor of abscess formation, with and without adequate nutrition, to determine if possible the relationship between a massive outpouring of leukocytes and serum with the subsequent loss of protein and its effect on the production of edema. As previously noted, abscess formation was produced by injection of turpentine subcutaneously. In each instance a large abscess was formed which subsequently broke down and drained profusely.

The experiment on cat 18 fortunately forms an interesting link between the preceding group, in which an attempt was made to study the drainage alone, and this group, in which the effect of a profuse purulent discharge was studied.

CAT 18.—This animal was given the diet containing 0.3 Gm. of nitrogen for thirty-four days before a drain was inserted into the abdomen. Then daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet. Subcutaneous injections of turpentine into the abdomen were begun twenty days after the drain was inserted, as at this time the drain had been pushed out and the incision had healed. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.6	7.1	3.2	34	690	70	38	...	.....
	Drain inserted								
6	2.4	6.7	3.0	25	672	70	38	...	.....
9	...	5.7	3.1	32	614	..	..	...	.....
13	Edema								
13	2.2	5.8	2.7	27	643	70	33	...	.....
16	2.1	6.2	2.6	35	655	..	..	...	.....
20	2.0	4.8	2.3	27	643	60	20	220	.....
	Edema gone, drain out and turpentine injected								
23	Edema								
23	1.9	4.9	1.2	20	660	55	18	215	2,021
26	1.5	...	...	..	...	..	..	115	2,150
27	1.8	4.7	2.0	26	643	55	12	200	2,000
28	1.7	...	...	..	...	..	..	265	1,934
29	1.7	...	...	..	...	..	..	187	1,350
30	1.7	4.4	2.2	27	655	45	10	165	1,551

Autopsy revealed the paws and chest to be very edematous. There was no fluid or infection in the abdominal cavity, and everything appeared to be normal. The lungs were very moist, and the pericardial sac contained a large amount of fluid. On analysis the pus from the abscesses showed: total protein, 7.6 Gm.; albumin, 0.65 Gm.; nonprotein nitrogen, 43 mg., and sodium chloride, 482 mg. The water content of the tissues (per cent) was: heart, *82.2*; lungs, *84.5*; liver, *81.0*; kidney, *83.2*; pancreas, *78.3*; pylorus, *83.5*; midileum, *80*; ileum, *80.8*; abdominal wall, 69.1; leg muscle, *82.7*.

There was profuse drainage with the development of definite edema in the legs in twelve days. The edema persisted until the drain was pushed out and the incision healed. Three days after the injections of turpentine were begun, the edema reappeared and increased in amount. There was profuse drainage from the abscesses. Toward the end of the experiment it was noted that when blood

was taken from a vein the cat tended to bleed profusely and that the blood did not clot readily. Death probably occurred from hemorrhage from one of the ear veins.

In view of the preceding experiment the following experiments were planned in order to note the effect of a variation in diet and hypodermoclyses in conjunction with the production of superficial sepsis.

CAT 32.—This animal was given the diet containing 1 Gm. of nitrogen for one day. It had been receiving an adequate diet before that. Subcutaneous injections of turpentine were made into the abdomen. No food or hypodermoclyses were given after the abscesses formed. The cat gradually grew weaker and died, fourteen days after the injections were started. Much thick creamy pus drained from the abscesses. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
Initial	3.4	7.5	3.7	33	672	80	..
5	2.9	6.2	2.9	54	655	70	27
10	2.4	5.5	3.6	126	555	60	37

Autopsy revealed no fluid in the abdominal, pleural or pericardial cavities. The intestine was filled with bile, and the stomach was greatly distended with gas. The gallbladder was greatly enlarged. The water content of the tissues (per cent) was: heart, *81.3*; lungs, 78.9; liver, *77*; kidney, *78.9*; pancreas, *83.1*; pylorus, *82.5*; midileum, *81.5*; ileum, *81.4*; abdominal wall, 76.5; leg muscle, 74.5.

This animal had an adequate diet until the subcutaneous injections of turpentine were given, but thereafter received only water by mouth. In ten days the serum protein dropped to the critical level, with a striking rise in the nonprotein nitrogen. Small amounts of water which could not be accurately measured were taken by mouth. Fourteen days after the first injection of turpentine there was no edema. However, weights of the tissues showed that there was an increase of water in the heart, pancreas, pylorus and ileum. It is probable that gross edema would have developed if the animal had been supplied with sufficient water. The terminal rise in nonprotein nitrogen coincided with a rise in the hematocrit reading and probably represented concentration from dehydration.

CAT 22.—This animal was given the diet containing 0.1 Gm. of nitrogen for thirty days prior to the injections of turpentine and continued to receive it after the injections were given. The cat lived for fifteen days after the first injection. It refused to eat seven days after the first injection. Much pus drained from the abscesses. A tabulation of findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent
Initial	1.6	6.5	2.5	30	690	65	28
7	...	6.5	2.5	33	614	65	22
12	1.4	6.8	...	36	693	60	18
15	1.1	6.8	3.4	41	565	60	18

The animal was killed because of weakness. Autopsy revealed that the abscess extended down both hindlegs; about 4 cc. of thick, creamy pus was removed. The abdomen and lungs looked normal. The analysis of the pus showed: total protein, 8.1 Gm.; albumin, 4.6 Gm.; nonprotein nitrogen, 120 mg.; chlorides, 437 mg. The water content of the tissues (per cent) was: heart, 76.7; lungs, 82.3; liver, *77*; kidney, 76.4; pancreas, *76.8*; pylorus, 78.2; midileum, 77.3; ileum, 78.1; abdominal wall, 64.4; leg muscle, *79.2*.

The liver revealed central congestion, and the kidneys showed moderate fatty vacuolation of the tubular epithelium.

A factor of undernutrition was present at the beginning of this experiment owing to an insufficient nitrogen diet for the preceding month. The same diet, containing 0.1 Gm. of nitrogen, was continued after the injections of turpentine.

At the end of fifteen days the cat was killed and, as in the preceding experiment, no edema was noted. A determination of the weights of the tissues showed an increase in the fluid content of the pancreas and the leg muscle. As in cat 32, it would seem that the lack of fluid intake was an important factor in the failure to produce edema. There was obviously a marked loss of protein in the drainage material from the abscesses.

CAT 25.—This animal was given the diet containing 1 Gm. of nitrogen for thirty-three days before injections of turpentine were started; then 200 cc. of 5 per cent dextrose in saline solution given daily by hypodermoclysis was added to the diet. The cat ate well, but gradually became weaker. Edema of the paws occurred fifteen days after the first injection of the turpentine. The next day the edema became massive and included all the extremities and shoulders. From this time until death the edema gradually decreased, and the volume of urine excreted increased. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	4.1	7.5	2.3	30	643	75	36	110	1,540
5	4.1	6.9	3.6	25	655	60	23	265	2,332
8	3.9	6.7	3.2	30	643	70	24	200	2,600
16	4.0	5.3	2.8	30	640	65	20	50	320
18	3.8	...	...	..	...	..	..	305	2,275
19	3.5	6.0	3.0	50	614	55	15	300	2,220

The cat died twenty-one days after the first injection of turpentine. The paws were edematous, and the skin and muscles were very juicy. No fluid was found in the abdominal, pleural or pericardial cavities. There was a large abscess on the abdomen. The water content of the tissues (per cent) was: heart, *80.6*; lungs, 81.3; liver, 68.6; kidney, 75.8; pancreas, *78.8*; pylorus, 79.2; midileum, *81.9*; ileum, *84.3*; abdominal wall, *78.6*; leg muscle, *79*. There was slight edema of the abdominal wall and leg muscle. The liver showed extensive degeneration, and the kidney showed extensive degeneration of the tubular epithelium.

Before receiving the injections of turpentine the animal was given an adequate diet which was supplemented with daily hypodermoclyses after the formation of an abscess. Gross edema developed fifteen days after the initial abscess formed, and associated with this was a striking drop in serum protein. There was also urinary retention associated with the development of the edema, but it is of interest that the excretion of urine increased until there was a positive diuresis at the end of the experiment. Six days after the development of the edema the cat died. At that time the paws were very edematous, and the skin and muscles were juicy. There was no accumulation of fluid in the serous cavities, but the weights of the tissues indicated a definite excess of water in the heart, lungs, ileum and muscles as well as in the subcutaneous tissue. The water content of the liver was extremely low; the liver showed definite degeneration on histologic examination. In some of the animals the liver was pale and revealed slight cellular changes. It is of interest that in this experiment urinary retention played only a transient rôle in the production of edema, and undernutrition probably was a minor factor. The caloric and nitrogen intakes were nearly satisfactory until the death of the animal.

It would seem that sepsis and a relatively large fluid intake were the important factors associated with the drop of the serum protein and the development of the edema. It is impossible to measure the importance of injury to the liver in this respect, but it is highly probable that this also constituted a factor of major importance.

CAT *26.*—This animal was given the diet containing 1 Gm. of nitrogen for eighteen days before the injections of turpentine. Daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline solution were substituted for the diet after the injections were started. Edema of the paws developed four days after the first injection. The cat lived for twenty-one days after the first injection. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	3.5	6.0	2.5	35	672	85	37	100	1,120
5	3.1	6.4	3.4	20	555	..	..	247	3,952
10	3.3	5.8	3.2	33	643	70	34	74	750
11	2.9	...	...	..	...	..	..	510	5,100
16	2.2	4.3	2.0	43	751	70	41	290	2,376
19	2.2	5.1	2.9	40	585	65	35	150	1,280

The paws and chest were edematous and there was questionable edema of the colon and ileum. From 5 to 10 cc. of ascitic fluid was found in the abdomen, while the lungs, though very moist, contained no definite fluid. The edema reached its peak after seventeen days and then receded until death. The water content of the tissues (per cent) was heart, *82;* lungs, 80.8; liver, *79.9;* kidney, *78.7;* pancreas, *82.5;* pylorus, 81.1; midileum, *81.8;* ileum, *82.5;* abdominal wall, *83.1;* leg muscle, *81.* There was moderate edema of the leg muscle and the abdominal wall, and the pancreas showed moderate edema of the interstitial tissue.

In this animal peripheral edema developed four days after the first injections of turpentine, and in this respect the results differ from those in most of the preceding experiments. The more rapid development of edema in this instance may be due to the effect of sepsis plus large hypodermoclyses augmented by starvation. It is of interest to note in this connection that edema developed in the face of a definite diuresis before any drop in the serum protein was noted. As the experiment continued there was evidence of diminished urinary activity and a drop in the serum protein and serum albumin to a low level. This coincided with the longest period of most marked edema. As in the preceding case, there was a slight terminal rise in the serum protein and a drop in the serum chlorides. Examination of the tissues showed an increase in the fluid content of the heart, lungs, pancreas, pylorus and ileum as well as of the muscles and subcutaneous tissues.

CAT 34.—This animal was given the diet containing 0.1 Gm. of nitrogen diet for twenty-one days before it received injections of turpentine. Afterward daily hypodermoclyses of 200 cc. of 5 per cent dextrose in water were substituted for the diet. Slight edema of the legs appeared five days after the hypodermoclyses and injections were started. The cat was found dead in the cage eight days after the injections began. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Nonprotein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.7	6.0	3.9	20	...	70	37	135	5.8
1	2.7	...	...	..	...	..	..	0	...
2	2.8	6.6	5.0	30	541	75	34	190	9.5
6	2.5	...	...	..	...	..	..	0	...

Autopsy showed an extensive abscess on the abdomen, but no penetration into the abdominal wall. There was no fluid in the abdomen or lungs, but the pericardial sac was filled with a clear yellow fluid. The legs and chest were edematous. The blood serum was icteric. The water content of the tissues (per cent) was: heart, *81*; lungs, 81; liver, *79.7*; kidney, *78.5*; pancreas, *72.4*; pylorus, 79.4; midileum, *80.9;* ileum, *81.3;* abdominal wall, *73.5*; leg muscle, 79.

This experiment differed from the others in that the fluid injected contained no sodium chloride. Edema developed five days after the injections of turpentine and the hypodermoclyses were started, the animal having had an insufficient nitrogen diet for three weeks. With the exception of a possible slight increase in the water content of the heart, lungs and ileum and a more than normal amount of fluid in the pericardial sac there was no abnormal accumulation of fluid in the tissues. The total volume of urine was diminished, and anuria was present on two of the last four days of the experiment. Coincidentally there appeared to be a concentration of the blood which kept the serum protein as well as the hemoglobin and the hematocrit values at the normal level. It is probable that more striking retention of fluid would have occurred if the animal had survived. These findings are to be compared with those of the following experiment.

CAT 28.—This animal was on the diet containing 0.1 Gm. of nitrogen for twenty-one days before the injections of turpentine began, after which daily hypodermoclyses of 200 cc. of 5 per cent dextrose in saline were substituted for the diet. There was massive edema of all dependent portions of the body thirteen days after the injections were started. A tabulation of the findings follows:

Days	Weight, Kg.	Serum Protein, Gm.	Albumin, Gm.	Non-protein Nitrogen, Mg.	Sodium Chloride, Mg.	Hemoglobin, per Cent	Hematocrit, per Cent	Urine Volume, Cc.	Urine Sodium Chloride, Mg.
Initial	2.3	6.5	3.1	38	614	85	38	100	.....
5	2.3	6.0	3.3	29	590	60	20	270	1,280
12	1.9	5.9	3.6	26	672	55	15	195	1,911
15	1.9	...	...	..	...	..	..	35	511
16	2.0	...	...	..	...	..	..	75	1,095

Autopsy showed edema of the paws, legs and buttocks and a slight excess of fluid in the abdomen and in the lungs. Everything else was normal. The water content of the tissues (per cent) was: heart, *83.4*; lungs, *85.1*; liver, *81.7*; kidney, *83.3*; pancreas, *83.5*; pylorus, 80.8; ileum, *81.9*; abdominal wall, *81.3*; leg muscle, *80.3*. The abdominal wall and the mucosa of the ileum showed edema. The villi were also edematous.

In this experiment an attempt was made to reproduce the sequence of events in cat 34 with the addition of sodium chloride to the fluid injected. This animal survived fifteen days instead of five, and although edema did not occur until eight days after the injections began, it was more generalized both peripherally and in the tissues. Without exception all tissues were water-logged. Toward the end of the experiment the serum protein was definitely lowered, and there were oliguria and chloride retention. This experiment showed a striking accumulation of fluid in the tissues as a result of undernutrition, pus formation and the administration of somewhat excessive amounts of fluid and sodium chloride.

It is of interest to speculate why edema did not develop more rapidly in cat 28, which received hypodermoclyses of dextrose and saline solution, than in cat 34, which received clyses of dextrose in distilled water. This is in disagreement with most experimental results, but the discrepancy may be due to the fact that anuria

developed in cat 34 almost immediately after the onset of the experiment. Such a disturbance of the renal function undoubtedly contributed to the more rapid formation of edema.

GENERAL COMMENT

From the foregoing experiments it is evident that by various maneuvers we have been able to produce in animals what may be described as a generalized disturbance associated with an abnormally high water content of the tissues. This edema, produced experimentally, involved not only the subcutaneous tissues, but also the muscles of the heart, lungs, pancreas, pylorus, jejunum, ileum, leg muscles, kidneys and liver. In some of the experiments only certain viscera were involved, and as a rule the heart, intestine, kidneys and pancreas were the first to show edema. In addition, free fluid was noted at times in the pleural, pericardial and peritoneal cavities in appreciable amounts. That such abnormal accumulation of fluid in the tissues is associated with other striking physicochemical changes is highly probable, but the scope of the present experiments limited our studies to the demonstration of edema of the tissues. The edema produced in our studies probably represented what is usually classified as nutritional edema, but our results seem to indicate clearly that undernutrition is only one of several important contributory factors.

Of the factors that we were able to control to a fairly satisfactory degree the following may be noted: general nutrition, from the point of view of caloric requirements; the intake of nitrogen, sodium chloride and water, respectively; the absorption of nutritive material from the gastro-intestinal tract; serous drainage; abscess formation, and, to a certain extent, surgical shock following general anesthesia and an abdominal operation. Factors which seemed to be secondary to those listed and which were beyond our control were those related to hepatic and renal insufficiency. The factors that were approximately under our control were those frequently encountered in operative conditions, particularly in those involving operations on the gastro-intestinal tract. For this reason we attempted to vary all of these factors within the limits commonly found in surgical practice.

As was to be expected from previous observations, the factor of undernutrition, and particularly that of nitrogen starvation, was of fundamental importance. It is equally clear that an adequate fluid intake was essential, even in the presence of nitrogen starvation of long standing, before edema would develop. With the exception of the experiments in which the animals were maintained on diets containing only 0.1 Gm. of nitrogen per kilogram of body weight, edema did not develop until after malnutrition was far advanced, provided no other factors were introduced. When the lack of nitrogen was acute, however, water tended

to accumulate in the tissues more rapidly, provided the fluid intake was considerable. It is evident, however, that the administration of somewhat excessive amounts of fluid was not the only important factor, at least under the conditions of our experiments. Excessively large amounts of fluid, amounting to several times the quantities used in our studies, will undoubtedly produce edema rapidly even in the absence of other factors. In the experiment on cat 18, however, we gave daily hypodermoclyses of approximately 80 cc. per kilogram of body weight, or the equivalent of more than 5 liters in a man of average weight. In the presence of deficiency of nitrogen and a fluid intake of such proportions edema did not develop in this animal until other factors such as serous drainage and sepsis were introduced. In this respect the observations of Atkins and White[6] on the rapid administration of enormous quantities of salt solution to normal and sick animals are of interest. In their studies the slow, continuous intravenous injection of 1,200 cc. of physiologic solution of sodium chloride in healthy cats produced edema of marked degree after ten hours. In an animal suffering from an acute infection a similar maneuver produced a much greater accumulation of fluid in the tissues as indicated by measurements of the water content of the tissues. Such acute experiments, however, bear only a slight analogy to our own, which more nearly approximated actual clinical conditions.

The influence of large amounts of sodium chloride on the production of edema is not strikingly indicated in our experiments, but has already been recognized by numerous investigators. At best it is only one important variable and is probably of little importance unless combined with other factors. In practically all of our animals the level of blood chlorides was usually well above normal and frequently was in the neighborhood of 700 mg. per hundred cubic centimeters. Therefore, there was practically always available an excessive amount of base capable of holding water in the tissues. In a few instances low figures for sodium chloride were obtained, but these were always terminal findings and probably were of little significance in the immediate problem. A study of the electrolyte concentrations in blood and tissues in conditions similar to those produced by us would have been of undoubted interest, but was beyond the scope of our investigation.

Our findings regarding the relation between the level of serum protein and serum albumin and the development of edema are in accord with numerous clinical observations. Undoubtedly there was a much greater tendency toward an abnormal accumulation of fluid in the tissues when the values for serum protein and serum albumin were at or below the so-called critical levels, as determined by Moore and Van

6. Atkins, J., and White, J. C.: Unpublished data.

Slyke.[7] When the serum protein was in the vicinity of 5.5 per cent or below, or the serum albumin at or below the level of 2.5 per cent, peripheral edema was frequently noted. At such times it was nearly always true that marked undernutrition was present which was associated with the depletion of nitrogen. At times it would appear that a lowering of the serum protein or serum albumin was due merely to the effect of rapid dilution by fairly large amounts of salt solution given subcutaneously, although it is safe to assume that in nearly every instance tissue protein was already markedly depleted. A careful examination of the protocols shows that in numerous instances peripheral edema and visceral edema of marked degree occurred in the presence of normal values for serum protein and albumin. Here again is a factor of variable importance in the production of edema. By itself it is incapable of causing abnormal accumulation of fluid in the tissues.

The importance of serous drainage as a factor in producing edema is strongly suggested by the experimental results. In the group of experiments in which drainage of the peritoneal cavity was instituted this procedure tended to hasten the accumulation of fluid in the tissues. In most of the experiments in this group there was some infection around the end of the drain, but this was certainly a late development and probably played very little part in the picture. In cat 18, however, we were fortunate enough to be able to study the effect of uncomplicated drainage of the peritoneal cavity. Drainage was profuse for a time, and during this period edema developed with an associated lowering of the serum protein to below the critical level. Coincident with a subsidence of drainage and a final removal of the drain, the edema disappeared. The obvious conclusion is that serous drainage contributed to the development of the edema. Attempts to collect the drainage fluid were unsuccessful, but analysis of the ascitic fluid found in three of the animals at autopsy showed protein contents of 0.9, 4.5 and 6.6 per cent, respectively. It seems highly improbable that the actual loss of protein occasioned by drainage of any of the fluids would in itself seriously alter the serum protein content under normal conditions. In association with marked undernutrition, and the administration of moderately large amounts of fluid and salt, it is entirely possible that such a loss of protein was of real importance in the production of edema, probably through a lowering of the serum protein.

The rôle of sepsis seems to be of extreme importance in our experimental results; it appears to explain the occurrence of edema noted in the cases of gangrenous appendicitis previously referred to. Like

7. Moore, N. S., and Van Slyke, D. D.: Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1929.

all the other factors already mentioned, excessive drainage of purulent material alone would probably be insufficient to produce marked edema, but when combined with the administration of saline solution in sufficient amounts and nitrogen depletion it seemed to be associated with striking results. Even in the absence of large amounts of fluid administered by hypodermoclysis edema of the tissues was demonstrable (cat 32 and 22), and when clyses were given, extensive edema developed. That it could be a determining factor is apparently illustrated in the experiment on cat 18. Here, with a constantly excessive fluid intake and nitrogen starvation edema appeared first with the establishment of serous drainage and disappeared when drainage ceased. It reappeared as massive anasarca when abscess formation was instituted. There are two possible explanations of the effect of abscess formation. The obvious one is that there was a striking and constant loss of nitrogenous material in the pus, with a consequent lowering of the serum protein. Analyses of samples of the purulent material collected from the abscesses gave values as high as 8.1 per cent protein and 4.6 per cent albumin. Especially in conditions of nitrogen starvation the loss of such amounts of protein might well contribute to an already existing nitrogen depletion.

In addition, however, it is interesting to consider the general effects of sepsis, as such. It is possible that there is a constant general reaction of the body to histamine or histamine-like substances in the presence of abscess formations with resulting increased capillary permeability. Under such conditions lack of nitrogen and a somewhat excessive fluid intake might result in a striking accumulation of fluid in the tissues. The increased water content of the tissues noted in the acute experiments already referred to, when animals suffering from an acute infection of the respiratory tract were used, strongly supports such a conception. The rôle of sepsis may therefore be a dual one, combining the factors of loss of protein and increased capillary permeability. It is possible that general anesthesia and surgical procedures may also play an analogous rôle to sepsis by means of transient effects on capillary permeability. Our experiments offer no evidence that this is true, but it is of interest to conjecture on the importance of such a factor in relation to major surgical procedures in badly depleted patients.

In addition to the factors just mentioned two other factors must be noted which undoubtedly played an important part in the production of edema. Urinary retention of water and sodium chloride was noted on many occasions. At times it was a transient phenomenon, and marked edema occurred in several instances when there was excellent diuresis. On the other hand, whenever retention was present, marked edema was usually noted. Complete anuria was noted twice. As a rule, diminished

urinary secretion was noted in association with the greatest degrees of nitrogen depletion. Disturbances of hepatic function could not be measured, but the appearance of the liver at autopsy strongly suggested that there were hepatic changes. Histologically, moderate degrees of necrosis were noted in the livers of several animals in which abscesses had been produced. As the glycogen content of the liver was undoubtedly depleted in practically all of the animals because of starvation, and probably because of sepsis, it is not unreasonable to suppose that normal water balances in the body were somewhat disturbed as a result.

As far as the relative importance of each of these factors in the production of edema is concerned, it is of interest to glance at tables

TABLE 4.—*Findings at the Onset of Edema*

Cat	Initial Diet, Gm. of Nitrogen per Kg. of Body Weight	Procedure Following Initial Diet	Day Edema Was Noted	Daily Hypodermoclyses, Cc. per Kg. of Body Weight	Daily Sodium Chloride, Gm. per Kg. of Body Weight	Blood Chemistry: Serum Protein, Gm. per 100 Cc.	Blood Chemistry: Serum Albumin, Gm. per 100 Cc.	Blood Chemistry: Serum Chlorides, Mg. per 100 Cc.	Urinary Retention
30	1.0	Anastomosis	28	60	0.53	5.1	1.9	687	+++
5	1.0	Anastomosis	27	24	0.23	5.7	3.4	655	++
11	1.0	Anastomosis	23	68	0.60	4.3	2.0	624	0
15	1.0	Anastomosis	20	66	0.60	4.9	2.7	660	±
33	0.1	.....	17	64	0.59	6.0	3.6	544	+
25	1.0	Abscess	15	45	0.45	5.3	2.8	640	++
28	0.1	Abscess	13	74	0.66	5.9	3.6	672	+++
18	0.3	Drainage	12	80	0.72	5.8	2.7	654	..
27	0.1	.....	11	64	0.58	5.9	3.0	690	0
34	0.1	Abscess	5	71	0.64	6.6	5.0	541	0
26	1.0	Abscess	4	50	0.45	6.4	3.4	555	0
18	...	Abscess	2	80	0.72	4.9	1.2	660	+
13	0.1	Anastomosis, drainage	2	60	0.54	4.3	3.3	672	++++
14	0.1	Anastomosis, drainage	2	60	0.54	(5.8)	...	...	++++

4 and 5. It seems obvious that edema developed most rapidly in those animals in which the most marked depletion of nitrogen was present. When this was combined with sepsis, drainage or an entero-anastomosis, edema occurred with extreme rapidity. The relative amounts of water and salt administered seemed to play a much less important rôle. Interference with the proper absorption of food resulted in the formation of edema only after a much longer period of time. The factor of urinary retention was important but inconstant. The level of serum protein and serum albumin was of importance only at times. The degree of water retention in the tissues also seemed to depend largely on the degree of undernutrition, especially in the presence of sepsis, serous drainage or a recent surgical procedure. Of all the factors nitrogen starvation and sepsis seem the most important, but only when combined with the administration of sufficient fluid and salt.

It is of some interest to consider the possible clinical significance of the edema noted in the various important viscera. Under ordinary

circumstances the term edema is used to denote an abnormal accumulation of fluid in the subcutaneous tissues. Pulmonary edema and effusions into the serous cavities are also recognized clinically. However, one does not ordinarily think of edema as occurring in such organs as the heart, intestines, pancreas and kidneys. Yet our findings give fairly conclusive proof that water can accumulate to a rather striking degree under proper conditions in any of the parenchymatous organs. It is unfortunate that we did not study the brain tissues in the experimental animals, as several showing marked edema elsewhere had convulsions, appeared disoriented and may well have had cerebral edema. The frequency with which an increase in water content was noted in the heart

TABLE 5.—*Findings at Death*

Initial Diet, Gm. of Nitrogen per Kg. of Body Weight	Procedure Following Initial Diet	Day Edema Was Noted	Duration of Life, Days	Daily Hypodermoclyses, Cc. per Kg. of Body Weight	Daily Sodium Chloride, Gm. per Kg. of Body Weight	Blood Chemistry: Serum Protein, Gm. per 100 Cc.	Blood Chemistry: Serum Albumin, Gm. per 100 Cc.	Blood Chemistry: Serum Chlorides, Mg. per 100 Cc.	Urinary Retention	Tissue Edema	Peripheral Edema
Cat											
30 1.0	Anastomosis	28	28	60	0.53	5.1	1.9	687	+++	+++	+
5 1.0	Anastomosis	27	29	24	0.23	6.5	1.9	707	0	+	±
11 1.0	Anastomosis	23	23	68	0.60	4.3	2.0	624	++	+	+
33 0.1	.....	17	17	64	0.59	6.0	3.6	544	+	++	++
25 1.0	Abscess	15	21	45	0.45	6.0	3.0	614	0	+	+
28 0.1	Abscess	13	15	74	0.66	5.9	3.6	672	+++	+++	++++
18 0.3	Drainage abscess	12	31	80	0.72	4.4	2.2	655	0	++	++
27 0.1	.....	11	23	64	0.58	7.2	4.9	526	0	+	+
34 0.1	Abscess	5	8	71	0.64	5.8	4.7	450	++++	++	++
26 1.0	Abscess	4	21	50	0.45	5.1	2.9	585	0	++	+
13 0.1	Drainage abscess	2	3	60	0.54	4.3	3.3	672	++++	+++	++
14 0.1	Drainage abscess	2	2	60	0.54	(5.8)	Dead	...	++++	+++	++++

was striking and, to us, surprising. In many instances the increases were slight, but in several animals they amounted to 4 or 5 per cent and in rare instances to as much as 10 per cent. Such a change represents a marked alteration of the physiology of the tissues, and one wonders seriously whether similar changes in the heart and other viscera may not so alter the functions of these organs as to interfere seriously with homeostasis. Under such conditions the circulatory, urinary, hepatic and digestive systems, for example, may all be somewhat disturbed and, from a lack of correct individual functioning, may fail to coordinate properly among themselves. The diarrhea which occurred in several of the animals, for example, appeared always to be a concomitant of edema of the intestinal tract. With diarrhea all the nutritional processes were manifestly upset, and a vicious circle was at once established. One is led to speculate whether various maneuvers such as the administration of a general anesthetic, surgical operations and the administra-

tion of narcotics may be followed in depleted patients by results utterly different from those obtained in patients in better condition. It is not reasonable to suppose that the cardiorespiratory apparatus, for example, will function normally with an excessive amount of water in the muscles of the heart and lungs. Urinary retention may well be aggravated by the existence of an already edematous kidney. The similarity of the so-called beriberi heart to the condition of edema of the heart muscles in our animals is notable. In other words, from the very existence of conditions such as we have produced in our experimental animals, we can readily conceive of the difficulties which may face the depleted preoperative patient when subjected to any major surgical procedure which necessarily involves further depletion, surgical shock, hypodermoclyses and possible surgical drainage. Obviously measures tending to maintain nutrition must be instituted, and the dangers of flooding the patient with excessive amounts of water and salt must be minimized as much as possible.

SUMMARY AND CONCLUSIONS

1. In a group of animals we have produced experimentally edema of the subcutaneous tissues and the viscera by measures simulating those not infrequently practiced on patients undergoing operations.

2. The production of edema appears to depend on certain factors which we have been able to vary independently. These factors, in the order of importance, seem to be nitrogen starvation, general malnutrition, sepsis, the administration of somewhat excessive amounts of water and sodium chloride, serous drainage, major surgical procedures and general anesthesia. Disturbances of renal and hepatic function play important rôles, but are secondary to the other factors.

3. The lowering of the serum protein and of the serum albumin is of importance in tending to make fluid accumulate in the tissues, but edema can readily occur in the presence of normal values.

4. The abnormal accumulation of water in the solid viscera has been noted and has been discussed in relation to homeostasis.

5. We have discussed the importance of our findings in their clinical application to the problem of the preoperative patient who is a poor risk.

GASTRO-INTESTINAL STUDIES

III. DETERMINATIONS OF ENZYMES ON AUTOPSY SPECIMENS FROM CASES OF PERNICIOUS ANEMIA AND PELLAGRA

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The importance of the deficiency in gastric secretion in the etiology of pernicious anemia has been established by the work of Castle and his associates. It is still a debatable question whether in this disease there is also a disturbance in the external secretory function of the pancreas. Anemia due to pancreatic disease has been sporadically described in the literature.[1]

Villa,[2] on the basis of the determination of fat, protein and trypsin in the feces, concluded that in pernicious anemia, depending on the severity of the disease, there is not only gastric achylia but also intestinal achylia and, in particular, pancreatic achylia. Landau and Glass [3] reported nine cases with both gastric and pancreatic achylia; however, they stated that the condition is rare. Cheney and Niemand,[4] as a result of determining trypsin in the gastric contents after fasting, believed that pancreatic insufficiency might be of etiologic importance in pernicious

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2. Villa, L.: La funzione del pancrease e l'achilia gastroenterica negli stati anemici: criteri diagnostici e dietetici, Clin. med. ital. **58**:295 (July-Aug.) 1927.

3. Landau, A., and Glass, J.: Achylia gastro-pancreatrici, Arch. f. Verdauungskr. **46**:192 (Oct.) 1929.

4. Cheney, G., and Niemand, F.: Possible Relationship of Pancreatic Insufficiency to Addison-Biermer (Pernicious) Anemia, Arch. Int. Med. **49**:925 (June) 1932.

anemia. On the other hand, Crohn,[5] Chace and Meyers,[6] White[7] and McClure and Jones[8] found normal or even increased amounts of pancreatic enzymes in the duodenal contents of the patients with pernicious anemia whom they examined. Fodor and Kunos,[9] although unable to find a case with pancreatic achylia, reported a decrease in diastase in the duodenal contents of patients with pernicious anemia.

Recently we[10] reported the results of the analyses of the duodenal contents of twenty-two patients with pernicious anemia. In every case pancreatic enzymes were found, although in some instances trypsinogen, especially, was present in decreased amounts. The patients with decreased amounts of trypsinogen showed moderate to advanced involvement of the central nervous system. To secure more data on the rôle of the gastro-intestinal enzymes in pernicious anemia, specimens of gastric and duodenal mucosa and of pancreatic tissue were secured at autopsy from patients who had had pernicious anemia. Since the gastro-intestinal symptoms in pellagra are sometimes similar to those associated with pernicious anemia, specimens were also obtained at autopsy from patients who had had pellagra. As a control specimens were obtained from persons who died of diseases other than pernicious anemia and pellagra and who did not show gastro-intestinal symptoms.

The gastric mucosa was analyzed for pepsin and rennin. The tryptic, lipolytic and amylolytic activity of the pancreatic tissue was estimated. The ability of the duodenal mucosa to activate trypsinogen was also determined.

METHODS

The Determination of Pepsin and Rennin in the Gastric Mucosa.—The gastric mucosa was scraped off with a knife, and a weighed quantity (from 5 to 6 Gm.) was placed in a flask with 50 or 100 cc. of 0.3 per cent hydrochloric acid and allowed to autolyze for three hours at 40 C. (104 F.) in order to activate the pepsinogen.

5. Crohn, B. B.: The Diagnosis of Functional Activity of the Pancreatic Gland by Means of Ferment Analyses of the Duodenal Contents and of the Stools, Am. J. M. Sc. **145**:393 (March) 1913; Studies in Pancreatic Disease, Arch. Int. Med. **15**:581 (April) 1915.

6. Chace, A. F., and Meyers, V. C.: The Examination for Diagnostic Purposes of the Enzyme Activity of the Duodenal Contents, Arch. Int. Med. **12**:628 (Dec.) 1913.

7. White, F. W.: Observations on the Use of the Duodenal Tube for Diagnosis and Treatment, Boston M. & S. J. **174**:674 (May 11) 1916.

8. McClure, C. W., and Jones, C. M.: Studies in Pancreatic Function; Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving Pancreas, Liver, and Stomach, Boston M. & S. J. **187**:909 (Dec. 21) 1922.

9. Fodor, I., and Kunos, I.: Funktionsuntersuchungen des Pankreas bei der Anaemia perniciosa, Folia haemat. **46**:93 (Dec.) 1931.

10. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Gastro-Intestinal Studies: II. Pancreatic Enzymes in Pernicious Anemia, J. Clin. Investigation **12**:519 (May) 1933.

The contents of the flask were then filtered through paper and the pepsin and rennin determined by the methods described previously.[11] The amount of peptic activity in 100 mg. of fresh mucosa was expressed in terms of 1:4,000 pepsin, U. S. P., and similarly the rennin activity of 100 mg. of fresh mucosa was compared to rennin, U. S. P.

The Determination of the Pancreatic Enzymes.—In removing the pancreas from the body, an effort was made to prevent the duodenal mucosa from coming in contact with the pancreatic tissue. The pancreas was then passed through a meat chopper and dehydrated and defatted by means of ice-cold acetone and ether. The mucous membrane of the duodenum was dehydrated and defatted in a similar way.

The lipolytic and amylolytic activity of the dried pancreatic tissue was estimated by the methods developed by McClure, Wetmore and Reynolds.[12] The amount of activity in 10 mg. of dry tissue was expressed in the units used by McClure.

The tryptic activity was determined on the pancreatic tissue before and after activation by enterokinase derived from duodenal mucous membrane of the individual patient examined and from the duodenal mucosa of swine. To activate the trypsinogen, 200 mg. of powdered pancreatic tissue and 100 mg. of powdered duodenal mucosa were weighed into a flask, and 100 cc. of fifteenth-molar phosphate buffer (p_H 7) was added. This mixture was allowed to incubate, with constant stirring, for thirty minutes at 40 C. It was then filtered, and 5 cc. of filtrate, corresponding to 10 mg. of dry pancreatic tissue, was used for the determination of tryptic activity by methods previously described.[10] To determine if the duodenum obtained at autopsy was fully able to activate the trysinogen, the pancreatic tissue was activated in the same way by means of enterokinase prepared from dehydrated and defatted duodenal mucosa from swine. The tryptic activity of 10 mg. of dry pancreatic tissue was expressed in milligrams of pancreatin, U. S. P.

RESULTS AND COMMENT

The results of the analyses are shown in the table. The absence of proteolytic enzymes in the gastric mucosa obtained from persons who died of pernicious anemia is a logical finding, since neither free hydrochloric acid nor enzymes can be elicited in the gastric secretion of such patients by any known gastric stimulant. These results might also explain why, except in rare instances, pepsin and rennin do not return in the gastric secretion of patients with pernicious anemia even after extensive treatment with liver or stomach preparations.

It was interesting to note that pepsin and rennin were present in the gastric mucosa of the pellagrins, although in smaller quantities than in the mucosa of the controls. The findings in case 6 were particularly significant, in that before death the gastric juice (obtained after stimu-

11. Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: Gastro-Intestinal Studies: I. Gastric Juice in Pernicious Anemia, J. Clin. Investigation **11**:1129 (Nov.) 1932.

12. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. **27**:706 (June) 1921.

lation with histamine) showed an absence of pepsin and rennin and was typical of that found in patients with pernicious anemia. It seems likely, therefore, that while histamine stimulation is adequate for the determination of the physiologic function of the stomach in most cases, it is not necessarily an absolute indication of a complete absence of pepsin and rennin in the gastric mucosa. This patient had a normal blood picture, and considering this fact, the presence of pepsin and rennin in the gastric mucosa might indicate that, although there was an absence of pepsin and rennin in the gastric juice, the "intrinsic factor of Castle" might still be present. Castle and his associates [13] have

Five Results of Analyses of the Gastric Mucosa for Pepsin and Rennin and the Determination of the Tryptic, Lipolytic and Amylolytic Activity of the Pancreas of Specimens Obtained at Autopsy *

				Gastric Mucosa, 100 Mg.		Pancreas, 10 Mg.				
						Trypsin in Mg. of Pancreatin, U. S. P.			Lipase in Cc. of N/10 Sodium Hydroxide	Amylase in Mg. of Dextrose
Patient	Age	Diagnosis	Gastric Analysis After Histamine	Pepsin in Mg. of Pepsin, U. S. P.	Rennin in Mg. of Rennin, U. S. P.	Before Activation	Activated with Duodenum (Autogenous)	Activated with Hog Duodenum		
1	59	Pernicious anemia	Achylia	0	0	0.8	5.0	4.2	5.9	4.1
2	70	Pernicious anemia	Achylia	0	0	0.9	5.4	5.2	1.5	1.5
3	52	Pernicious anemia	Achylia	0	0	1.2	5.0	4.5	1.3	1.1
4	53	Pellagra	.....	0.6	6	0.6	10.1	9.3	3.3	2.2
5	33	Pellagra	.....	0.9	..	1.3	6.6	5.6	1.6	3.7
6	57	Pellagra	Achylia	1.0	15	5.4	7.6	7.5	2.9	3.0
7	34	Pulmonary embolism	.....	3.8	35	0.4	7.4	8.0	4.0	4.0
8	39	Cardiac failure	.....	2.7	22	2.8	4.0	4.0	2.8	2.8
9	74	Cardiac failure	.....	1.3	20	2.5	5.5	5.1	1.3	2.0

* The specimens examined were obtained from twelve to fifteen hours after death, with the exception of those from case 3, which were obtained thirty-six hours after death.

shown that the "intrinsic factor" was present in four patients with achlorhydria. One had a normal blood picture and the remaining three had a microcytic type of anemia; therefore, the presence of pepsin and rennin does not necessarily mean that the intrinsic factor is always present. However, Wilkinson [14] has shown that in commercial prepara-

13. Castle, W. B.; Heath, C. W., and Strauss, M. B.: IV. Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia; Biologic Assay of Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or with Hypochromic Anemia Having no Free Hydrochloric Acid, and of Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, Am. J. M. Sc. **182**:741 (Dec.) 1931.

14. Wilkinson, J. F.: Activity of Commercial Preparations of Hog's Stomach, Brit. M. J. **1**:325 (Feb. 20) 1932.

tions of hog stomach the pepsin content usually parallels the hematopoietic activity. If the pepsin is destroyed, the hematopoietic activity is also lost.

The pancreatic tissue in every case compared favorably in enzymatic activity with pancreatin, U. S. P. Furthermore, the duodenal mucosa obtained at autopsy in every instance was able to activate fully the trypsinogen in the pancreatic tissue. There were no characteristic differences in tryptic, amylolytic or lipolytic activity in the types of cases studied. From these results we conclude that in patients with either pernicious anemia or pellagra the pancreas can form the principal pancreatic enzymes in good quantity, and that the duodenal mucosa can also produce enterokinase to activate the trypsinogen secreted by the pancreas.

CONCLUSIONS

1. The gastric mucosa obtained from three patients with pernicious anemia contained no pepsin or rennin.

2. Pepsin and rennin were present in the gastric mucosa of pellagrins, although in smaller quantities than in persons who died of cardiac failure and pulmonary embolism.

3. The pancreatic tissue from the persons with pernicious anemia and pellagra contained normal amounts of tryptic, amylolytic and lipolytic enzymes as compared with that from persons who had died of cardiac failure and pulmonary embolism.

4. The duodenal mucosa from persons with pernicious anemia and pellagra produced sufficient enterokinase to activate fully the trypsinogen of the pancreatic tissue.

Dr. H. C. Thornton assisted in securing the pathologic specimens.

ORIGIN AND SIGNIFICANCE OF TYROSINURIA IN DISEASE OF THE LIVER

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Disorders in the metabolism of tyrosine are observed in the inborn metabolic anomaly, alkaptonuria, and in so-called tyrosinosis. In the latter condition, tyrosine, dihydroxyphenylalanine, hydroxyphenylpyruvic acid and hydroxyphenyl acetic acid appear in the urine.[1] Tyrosine is occasionally found in the urine in cases of cystinuria.[2] Tyrosinuria may also occur independently of any anomaly of metabolism. The substance has been recovered in crystalline form from the urine of a normal subject [3] and in various pathologic conditions, mainly involving the liver and biliary passages.[4] The unreliability of the crystalloscopic method of diagnosis was emphasized in a previous communication.[5]

Frerichs and Städeler,[6] who first demonstrated the presence of leucine and tyrosine in the urine of a patient with acute yellow atrophy of the liver, established the basis for the belief that the amino-acids excreted in the urine in this disease are derived from the decomposition of the liver proteins. In view of the important rôle of the liver in the deamination of amino-acids, a disturbance of this function has also been held responsible for tyrosinuria.

In order to determine the clinical significance of tyrosinuria and to accumulate data which might throw light on its pathogenesis the following points were investigated: (1) the incidence of tyrosinuria in various hepatic and nonhepatic clinical disorders; (2) the amino-acid

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1. Medes, Grace: A Hitherto Undescribed Inborn (?) Error of Metabolism Related to Tyrosine, Abstr., J. Biol. Chem. **87**:XI, 1930; A New Error of Tyrosine Metabolism; Tyrosinosis; The Intermediary Metabolism of Tyrosine and Phenylalanine, Biochem. J. **26**:917, 1932.

2. Abderhalden, E., and Schittenhelm, A.: Ausscheidung von Tyrosin und Leuzin in einem Falle von Cystinurie, Ztschr. f. physiol. Chem. **45**:468, 1905.

3. Rosenbloom, J., and Gardner, W. E.: Tyrosine Crystals in the Urine of a Normal Pregnant Woman, New York M. J. **100**:574, 1900.

4. Bibliography cited by Rosenbloom and Gardner.[3]

5. Lichtman, S. S., and Sobotka, H.: An Enzymatic Method for the Detection of Tyrosine in Urine, J. Biol. Chem. **85**:261 (Dec.) 1929.

6. Frerichs, F. T., and Städeler, G.: Wien. med. Wchnschr. **4**:465, 1854; Arch. Anat., Physiol. u. wissensch. Med., 1856, p. 47.

content of the blood and urine in cases of tyrosinuria; (3) the tolerance for tyrosine as determined by feeding experiments on patients with disease of the liver; (4) the quantitative excretion of tyrosine in the urine, and (5) the relationship of tyrosinuria to jaundice and to the prognosis.

The tyrosinase method of Lichtman and Sobotka [5] reveals concentrations of 12.5 mg. per hundred cubic centimeters of tyrosine. The advantages of this method over the Frerichs-Städeler crystalloscopic method are economy of time and labor, specificity and sensitivity.

The amino-acid content of the blood and urine was determined by the colorimetric method of Folin.[7] Folin found that the amino-acid content of normal blood varies between 5 and 8 mg. per hundred cubic centimeters, and that of normal urine between 6 and 20 mg. per hundred cubic centimeters. β-naphthol-sulphonic acid was employed as the color reagent.

OBSERVATIONS

Clinical Incidence of Tyrosinuria.—Fifty specimens of normal urine previously examined by the tyrosinase method gave negative reactions.[5] The present study also includes observations on one hundred patients with diseases of the liver and bile passages and other conditions in which tyrosinuria has been described. The result of the study is as follows:

	Number of Cases	
	Total	Positive Reaction for Tyrosine
1. Hepatic and gallbladder disease		
Acute yellow atrophy	3	3
Subacute yellow atrophy	6	3
Catarrhal jaundice	12	2
Portal cirrhosis (alcohol), ascites	2	0
Portal cirrhosis (alcohol) with superimposed acute degeneration, burns	1	1
Cirrhosis of the liver, ascites, syphilis	2	2
Toxic cirrhosis (cinchophen)	7	1
Toxic hepatitis (arsphenamine), syphilis	11	2
Cholelithiasis, cholecystitis, cholangeitis, choledocholithiasis	10	2
Malignant disease of the gallbladder, bile passages and liver	19	6
Hemochromatosis	1	0
Weil's disease	1	0
2. Nonhepatic disease	25	1

7. Folin, O.: A New Colorimetric Method for the Determination of the Amino-Acid Nitrogen in Blood, J. Biol. Chem. **51**:377, 1922; A Colorimetric Determination of the Amino-Acid in Normal Urine, ibid. **51**:393, 1922.

Tyrosinuria occurred in approximately 30 per cent (22 of 75) of the cases of disease of the gallbladder, bile passages and liver. It occurred most frequently in patients suffering from acute and subacute degeneration of the liver and less frequently in patients with malignant disease of the liver and bile passages, obstructive jaundice due to stone, and toxic (from arsphenamine and cinchophen) or catarrhal jaundice.

In cases of pneumonia, leukemia, pernicious anemia and hyperthyroidism the results were negative. Five patients with jaundice complicating pneumonia, heart failure or leukemia had no tyrosine in the urine.

Tyrosinuria might be expected in the presence of extrahepatic parenchymal autolysis. In degenerating carcinoma of the lung tyrosine may be found in the sputum. It may appear in the urine if the degenerating process does not discharge its products through the bronchial tract.[8] Tyrosine, in amounts of 15 and 25 mg. per hundred cubic centimeters, was demonstrated in the urine of one of eight patients with pulmonary neoplasm studied in this series. Empyema and extensive metastases were also present. The metastases or the lung focus alone, or both, may have been responsible for the tyrosinuria. Metastases to the liver were present in the cases of tumors of the lung with tyrosine crystals in the urine reported by Asperger.[8]

The findings in a case (15) of arsenical dermatitis exfoliativa without icterus or morphologic changes in the liver gave definite evidence of an extrahepatic origin of tyrosinuria in some cases. On three occasions the patient excreted 32, 15, and 17 mg. of tyrosine per hundred cubic centimeters of urine. Despite the absence of jaundice, tests indicated impairment of hepatic function, such as usually accompanies and follows arsphenamine therapy. Some degree of hepatic insufficiency may be a requisite factor in tyrosinuria of extrahepatic origin. Extensive third degree burns may have contributed to the causation of the tyrosinuria in a case (12) of alcoholic portal cirrhosis with recently superimposed acute degeneration of the liver.

The Amino-Acid Content of the Blood and Urine in Cases of Tyrosinuria.—The amino nitrogen content of the blood was determined in seven cases of tyrosinuria. In only a single instance, a case (3) of acute yellow atrophy, was the amino nitrogen elevated (9 mg. per hundred cubic centimeters of blood).

The amino-acid nitrogen content of the urine was determined in six cases. In four, an elevation in the excretion of amino-acids was noted, the highest value being 40 mg. per hundred cubic centimeters (cases 3, 5, 9 and 15). The upper limit of normal excretion is recognized as 20 mg. per hundred cubic centimeters of urine.

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8. Asperger, H.: Leuzin und Tyrosin im Harn bei Lungengeschwulsten, Wien. klin. Wchnschr. **43**:1273, 1930.

Tyrosine and Amino-Acid Content of the Urine and Amino-Acid Content of the Blood in Tyrosinuria

Case	Patient	Clinical Diagnosis and Result	Date	Tyrosine, Mg. per 100 Cc. of Urine	Amino-Acid Nitrogen, Mg. per 100 Cc.	
					Blood	Urine
1	M. S.	Acute yellow atrophy (necropsy).....	.....	200	...	....
2*	.....	Acute yellow atrophy (fatal).....	.....	200 (approx.)	...	....
3	Dr. B.	Acute yellow atrophy.....	1/28	25	...	36.5
			1/30	100	9.0	35.0
4	G. P.	Subacute yellow atrophy (necropsy)	4/19	Negative	6.3	12.5
			4/21	Negative	6.1	....
			4/23	12.5	...	16.5
			4/24	Negative	...	....
			4/25	12.5	...	12.5
			6/ 3	Negative	...	....
			6/ 6	Negative	...	7.0 (ante mortem)
5	R. F.	Subacute yellow atrophy (necropsy)	3/16	Negative	...	....
			3/28	12.5	5.6	20.0
			3/30	Negative	...	22.5
			4/ 1	Negative	...	20.0
			4/24	....	6.5	....
			5/ 4 (ante mortem)	....	7.3	....
6	E. W.	Subacute yellow atrophy (necropsy)	10/28	16.5	6.0	....
			10/30	....	...	9.2
			10/31	....	...	10.9
7	M. S.	Catarrhal jaundice	11/27	Crystals	...	....
			11/30	Negative	...	....
8	J. F.	Catarrhal jaundice	1/13	15.0	...	....
			1/19	Negative	8.0	....
9	R. F.	Syphilitic hepatitis (secondary syphilis, recovery)	6/16	15.0	6.8	33.0
10	M. B.	Cirrhosis of the liver, ascites, syphilis; unchanged	.....	12.5 to 50.0	...	....
11	B. McK.	Cirrhosis of the liver, ascites, syphilis; unchanged	10/16	16.5	...	....
			10/21	30.0	7.3	....
			11/18	Negative	...	....
			2/ 1	Negative	...	....
12	J. H.	Portal cirrhosis (alcoholic), ascites, burns, acute degeneration (necropsy)	3/15	25.0	...	....
13	L. H.	Arsphenamine jaundice (recovery)...	.....	Crystals	...	....
14	Z.	Toxic cirrhosis (cinchophen) (recovery)	1/10	15.0	...	....
			1/17	Negative	...	....
			1/21	12.5	...	....
			1/24	Negative	...	....
15	S. L.	Dermatitis exfoliativa from arsphenamine, liver normal (necropsy)	2/10	32.0	...	17.0
			2/15	15.0	...	40.0
			2/17	17.0	...	30.0
			2/19	Negative	...	20.0
16	H. R.	Metastatic carcinoma of liver (necropsy)	.....	20.0 to 25.0	....	....
17	M. F.	Carcinoma of pancreas, metastases to liver (clinical)	3/ 4	15.0	...	....
			3/ 7	Negative	...	....
18	M. S.	Carcinoma of pancreas, metastases to liver (laparotomy)	3/18	15.0	...	....
19	C.	Carcinoma of cystic duct, metastases to liver (necropsy)	3/ 8	15.0	...	....
			3/10	Negative	...	....
20	H. S.	Carcinoma of lung, empyema, metastases to liver (necropsy)	1/14	15.0	...	....
			1/19	25.0	...	....
21	J. S.	Carcinoma of ampulla, metastases to liver (laparotomy); fatal	3/15	15.0	...	....
22	S. F.	Choledocholithiasis (laparotomy); recovery	3/31	15.0	...	....
			4/ 2	15.0	...	....
			4/ 7	Negative	...	....
23	S.	Postcholecystectomy choledocholithiasis (laparotomy); unchanged	4/ 4	25.0	...	....
			4/ 7	Negative	...	....

* Compare data with those of Schültzen and Riess.[8]

Two cases of subacute yellow atrophy with tyrosinuria showed a normal amino nitrogen content of the blood and urine.

The values for tyrosine are expressed in milligrams of amino nitrogen per hundred cubic centimeters. As tyrosine has 8 per cent of nitrogen, from 12.5 to 30 mg. of this single amino-acid per hundred cubic centimeters of urine would not appreciably elevate the total amino nitrogen content of the urine. The increased urinary amino nitrogen in the cases of slight tyrosinuria must therefore be due to the excretion of amino-acids other than tyrosine.

The findings in the cases of subacute yellow atrophy with transient minimal tyrosinuria suggest that tyrosine may constitute as much as one tenth of the amino nitrogen content of the urine. The share of tyrosine in the total amino-acids of normal urine must be considerably lower. In a case (3) of acute yellow atrophy the tyrosine nitrogen content of the urine constituted approximately one fourth of the total output of amino nitrogen.

Tyrosine Tolerance.—Tolerance for tyrosine was tested by administration of 2 Gm. of tyrosine in 100 cc. of hot water to each of three normal subjects. The urine collected in the following four hours contained no tyrosine. The same amount of tyrosine was fed to five patients with disease of the liver. All gave negative reactions. (These were cases of jaundice complicating pneumonia, arsenical hepatitis, toxic cirrhosis ascribed to cinchophen, stone in the common duct and subacute yellow atrophy in a child.) Thirty grams of a mixture consisting chiefly of monosodium glutamate was added to 2 Gm. of tyrosine and fed in 200 cc. of cold tomato juice to each of four subjects, one normal and three with jaundice. Of the latter, two had subacute yellow atrophy with a fatal outcome, and one had a stone in the common duct.

In only one case of subacute yellow atrophy (case 4) did the test give a positive reaction. Two grams of tyrosine fed to this patient did not produce tyrosinuria. One week later a test meal of 30 Gm. of the monosodium glutamate mixture and 2 Gm. of tyrosine fed to the same subject yielded 15 mg. of tyrosine per hundred cubic centimeters of urine collected in the following two hours and 12.5 mg. per hundred cubic centimeters in the urine collected in the succeeding two hours, suggesting the possibility of a diminished tolerance for this amino-acid in this type of hepatic disease.

Frequency of Occurrence and Quantitative Excretion of Tyrosine.—Tyrosine was found in the urine of three patients with acute yellow atrophy. Of twelve examinations of the urine in three cases of subacute yellow atrophy four revealed tyrosine. Of twenty-one examinations made in nineteen cases with malignant condition involving the liver,

seven gave positive reactions for tyrosine. Five of the six tests for tyrosine on two patients with extrahepatic foci of autolysis, in the skin and lung respectively, proved positive.

Except in cases of acute yellow atrophy minimal or moderate amounts of tyrosine, from 12.5 to 30 mg. per hundred cubic centimeters of urine, are excreted. Larger amounts are excreted only in acute yellow atrophy. In case 1, more than 1 Gm. of tyrosine was excreted in twelve hours, and in case 3, 0.9 mg. was excreted in twenty-four hours ante mortem. Death occurred on the fifth day of illness in an early stage of acute atrophy of the liver. In case 2 qualitative observations alone could be made. The intensity of the formation of melanin in the tyrosinase reaction, however, approximated that of case 1.

The inconstancy with which tyrosine crystals have previously been found in the urine in genuine cases of acute yellow atrophy of the liver is due to the limitations of the crystalloscopic method. With the tyrosinase method tyrosinuria is a constant finding in this disease. Its rapid course and rarity render it difficult to collect a large number of repeated observations. In subacute yellow atrophy, on the other hand, the more protracted course permits repeated tests. As the tyrosinuria in the subacute disease is slight, transient frequent tests must be made, or the tyrosinuria may be missed. This probably explains the negative findings in three cases of subacute yellow atrophy in this series, one fatal and one with recovery, in which only single examinations were made.

Relationship of Tyrosinuria to Jaundice and to Prognosis.—Jaundice was present in nineteen of twenty-three cases of tyrosinuria. In two of the four nonjaundiced patients extensive extrahepatic foci of autolysis were present, a carcinoma of the lung in case 20 and an extensive sloughing exfoliating dermatitis due to arsphenamine in case 15. Tyrosinuria was demonstrated in case 18 when obstructive jaundice due to malignancy had been completely relieved by cholecystogastrostomy. Tyrosine was present in the urine on two occasions in a case (14) of toxic cirrhosis ascribed to the action of cinchophen. A transitory icterus had entirely receded.

Eight of twenty-three patients with tyrosine in the urine (cases 7, 8, 9, 10, 11, 13, 14 and 22) recovered or remained in unchanged bodily condition. In all these instances, only minimal or moderate amounts of tyrosine were present in the urine.

COMMENT

The recovery of tyrosine from urine has been considered an ominous sign since the original observation of Frerichs and Städeler in a fatal case of acute yellow atrophy. Schultzen and Reiss [9] and I have recov-

9. Schültze, N. O., and Reiss, L.: Ueber akute Phosphorvergiftung und akute Leberatrophie, Ann. d. Char.-Krankenh. **15**:1, 1869.

ered massive amounts of tyrosine varying from 0.9 to over 2 Gm. from the urine in a period of twenty-four hours in acute cases of the disease. Massive excretion apparently indicates an acute diffuse degeneration of the liver. The excretion of tyrosine is continuous throughout the brief course of this illness.

On the other hand, temporary tyrosinuria, usually slight in amount, does not preclude recovery. In case 11, that of a patient with cirrhosis of the liver and syphilis, tyrosinuria accompanied massive ascites. An acute degenerative process was superimposed on an old cirrhotic lesion. Tyrosinuria vanished with the ascites. Similar observations have been made by Risak,[10] Geronne[11] and Hamne[12] in cases of degeneration of the liver. Patients with slight transitory tyrosinuria who recovered, suffered from hepatitis of syphilitic or arsenical origin, toxic cirrhosis, catarrhal jaundice or common duct stone. In subacute atrophy of the liver minimal or moderate tyrosinuria may cease, though the patient may eventually die of functional insufficiency of the liver.

In acute yellow atrophy the amounts of amino-acids lost in the urine are too large to be accounted for by functional impairment. My observations on tyrosinuria support the conception of Frerichs and the findings of Wells[13] and of Stadie and Van Slyke[14] who suggested that the abnormal amounts of amino-acids lost in the urine in acute yellow atrophy originate mainly from autolysis of liver tissue rather than from impairment of liver function. The normal amino nitrogen content of the blood and urine in some cases of minimal tyrosinuria (cases 4 and 5) furthermore indicates that the latter factor may be insignificant.

Röhmann,[15] who was unable to recover tyrosine from the urine of a patient with acute atrophy of the liver, maintained that amino-acids are excreted only when the rate of their formation exceeds that of their destruction in the body. Schültzen and Riess[9] and Rohmann isolated a deamination product of tyrosine, oxymandelic acid, from the urine in some patients with tyrosinuria. Minkowski[16] also believed

10. Risak, E.: Ueber das Vorkommen von Leuzin und Tyrosin im Harn, Med. Klin. **26**:666, 1930.

11. Geronne, A.: Zur Pathogenese einiger Formen des Ikterus, Klin. Wchnschr. **1**:828, 1922.

12. Hamne, B.: Die prognostische Bedeutung positiver Tyrosin und Leuzin Reaktion im Harn bei Hepatitis, Upsala läkaref.-förh. **38**:8, 1932.

13. Wells, H. G.: The Chemistry of the Liver in Acute Yellow Atrophy, J. Exper. Med. **9**:627, 1907.

14. Stadie, W. C., and Van Slyke, D. D.: The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, Arch. Int. Med. **25**:693 (June) 1920.

15. Röhmann, F.: Chemische Untersuchung von Harn und Leber bei einem Falle von akuten Leberatrophie, Berl. klin. Wchnschr. **25**:861, 1888.

16. Minkowski: Krankheiten der Leber und der Gallenwege, in von Merings, J.: Lehrbuch der inneren Medizin, Jena, Gustav Fischer, 1919, vol. 11, p. 645.

that the appearance of tyrosine in the urine depended on the rate of the degenerative process in the liver. The present quantitative observations with the tyrosinase method lend some support to this view.

It is clinically significant that tyrosinuria may occur occasionally in patients with long-standing obstruction of the common duct due to stone. Minimal amounts of tyrosine were excreted in the urine in case 22 on two occasions. Obstructive jaundice had existed for eight weeks. The patient was afebrile. The liver was swollen. There was no cholangeitis. Following cholecystectomy recovery was uneventful. Geronne [11] cited a similar instance of jaundice due to stone in the common duct with tyrosine crystals in the urine.

SUMMARY

Tyrosinuria was studied in health and in disease by the tyrosinase method. Its occurrence and estimation proved to be of significance in the diagnosis and prognosis of diseases of the liver and bile passages and in the interpretation of its mode of origin.

The quantitative observations in excretion of tyrosine confirm the view that the abnormal amounts of amino-acids excreted in the urine of patients with acute atrophy of the liver originate mainly from autolyzed liver tissue. While it is conceded that in acute diffuse degeneration of the liver the function of the liver in deamination may fail and contribute to the amino-aciduria, this factor plays only a minor rôle. Studies of the amino nitrogen content of the blood and urine in some cases of subacute atrophy of the liver with tyrosinuria indicates that in this less acute form of degeneration of the liver tyrosine may appear in the urine when there is no apparent disturbance in the metabolism of amino-acids.

Observations on the rate of excretion of tyrosine are of diagnostic significance. Continuous massive tyrosinuria occurs only in cases of acute yellow atrophy with a rapid and fulminant course. Transitory minimal and moderate tyrosinuria occurs in cases of subacute atrophy of the liver, in degenerating neoplasm of the liver, in toxic degeneration of the liver and uncommonly in obstructive jaundice of long standing due to stone. Inflammatory lesions of the bile passages do not of themselves give rise to tyrosinuria.

Extrahepatic foci of autolysis, such as degenerating tumors of the lung or extensive sloughs of the skin, may give rise to minimal or moderate amounts of tyrosine in the urine.

The transitory nature of minimal or moderate tyrosinuria is demonstrated by repeated tests. During the phase of recovery from degeneration of the liver, the products of parenchymal autolysis have already been absorbed, and tyrosine vanishes from the urine, but with a fresh

attack of degeneration of the liver, tyrosine reappears in the urine. In the stage of repair, namely in coarse nodular cirrhosis, or in the terminal stages of subacute yellow atrophy with a critical reduction in the functioning parenchyma of the liver, tyrosine may not be demonstrable in the urine.

Tyrosinuria may occur without jaundice either in cases of extrahepatic origin or in those of demonstrable disease of the liver.

Quantitative observations with respect to tyrosine are of prognostic value. In cases of minimal tyrosinuria the patients are more likely to recover, whereas cases of massive tyrosinuria terminate fatally in a short time. Mounting tyrosinuria indicates rapidly progressive degeneration of the liver. However, the absence of tyrosinuria in cases of degeneration of the liver does not warrant an optimistic prognosis.

EFFECT OF TOXEMIA ON TOLERANCE FOR DEXTROSE AND ON THE ACTION OF INSULIN

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AND

L. C. LoBELLO

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In a previous article,[1] attention was directed to the effect of toxemia on the tolerance for dextrose. Rabbits were given injections of varying doses of diphtheria toxin, and daily dextrose tolerance tests were made, 5 gm. of dextrose being used. It was shown that, as the toxemia increased from day to day, the tolerance for dextrose decreased. Some of the animals that survived as many as seven or eight days of the toxemia acquired blood sugar levels as high as 400 or 500 mg. two hours following the administration of dextrose. The exact explanation of this phenomenon is not clear. It may be observed in normal human beings who are toxic,[2] but is more strikingly seen in diabetic persons who are victims of infections. One of two explanations may be offered for such an effect on dextrose tolerance: (*a*) an increased glycogenolysis or (*b*) an inhibition of glycogenesis.

Lawrence and Buckley [3] suggested from similar experiments that glycogenolysis is activated through a thyro-suprarenal stimulation resulting from the toxemia. The second explanation seems to us to be more likely. This may occur in one of several ways: by a neutralization or inactivation of insulin by the toxemia; by some disturbance in the natural storehouses of glycogen; by a diminished oxidation of sugar; by a suppression of endogenous production of insulin, or by some combination of them.

A second study [4] was made in an effort to substantiate one of these views. Rabbits were intoxicated as in the first series of observations

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1. Sweeney, J. S., and Lackey, H. W.: The Effect of Toxemia on Tolerance for Dextrose, Arch. Int. Med. **41**:257 (Feb.) 1928.

2. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.) 1932.

3. Lawrence, R. D., and Buckley, O. B.: Inhibition of Insulin Action by Toxaemias and Its Explanation; Effect of Diphtheria Toxin on Blood-Sugar and Insulin Action in Rabbits, Brit. J. Exper. Med. **8**:1 (Feb.) 1927.

4. Sweeney, J. S.: Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, Arch. Int. Med. **41**:420 (March) 1928.

mentioned, and as the toxemia increased from day to day, a uniform dose of insulin was given (2 units) ten minutes after the daily administration of dextrose. We thought that a constant 2 unit effect of insulin

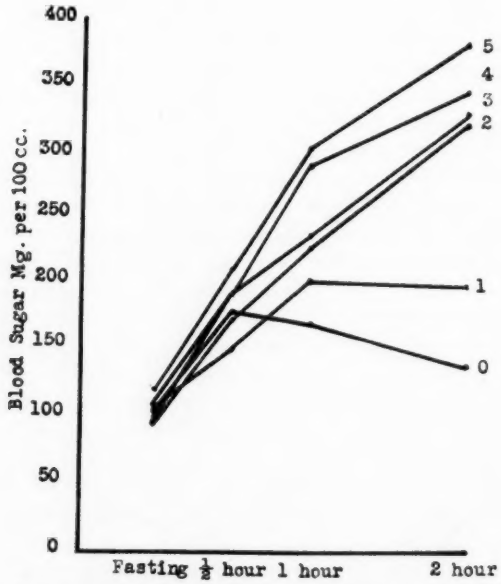

Chart 1.—Daily curves showing the tolerance for dextrose of rabbit 7 following a subcutaneous injection of 0.0075 cc. of diphtheria toxin (the minimum lethal dose equals 0.03 cc.). The numbers at the end of each curve indicate the day of toxemia.

TABLE 1.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit 7, Following the Subcutaneous Injection of 0.0075 cc. of Diphtheria Toxin (Minimum Lethal Dose Equals 0.03 Cc.)*

Hours of Starvation	Hours of Toxemia	Rectal Temperature, F.	Blood Sugar, Mg. per 100 Cc.			
			Fasting	After Dextrose, Min.		
				30	60	120
24	..	...	105	182	179	145
48	24	105	107	152	206	206
72	48	102	95	174	230	333
96	72	101	100	190	244	345
120	96	103	109	190	296	357
144	120	103	120	215	313	400

could be demonstrated, even as the toxemia increased, and it was suggested on the basis of these experiments that the effect of toxemia is that of a suppression of endogenous insulin.

The experiments to be reported in this study are similar to those just mentioned and were performed in an effort to get a better under-

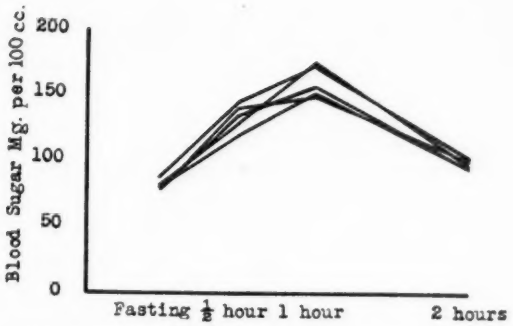

Chart 2.—Daily curves showing the tolerance for dextrose of rabbit D. Neither diphtheria toxin nor insulin was given (table 2).

TABLE 2.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit D* **

Hours of Fasting	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
24	None	83	131	179	101
48	None	82	123	154	100
72	None	80	140	158	100
96	None	80	143	152	105
120	None	88	148	175	107

* This rabbit received neither diphtheria toxin nor insulin (control). Five grams of dextrose was given daily.

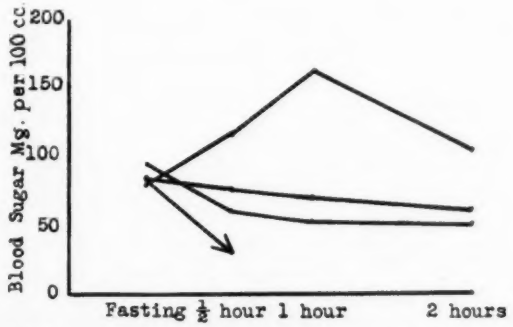

Chart 3.—Daily curves showing the tolerance for dextrose of rabbit A. No diphtheria toxin was given. Insulin in increasing doses (2 units) daily was given twenty minutes before 5 Gm. of dextrose was administered. The animal died in convulsions on the third day following the administration of 6 units of insulin (table 3).

TABLE 3.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit A* **

Hours of Fasting	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
24	0	80	117	165	105
48	2	87	77	71	69
72	4	93	63	57	51
96	6	83	Died in convulsions		

* This rabbit was given no diphtheria toxin, but daily increased doses of insulin were given twenty minutes before the daily administration of 5 Gm. of dextrose.

standing of the effect of toxemia on the action of insulin. Knowing that the tolerance for dextrose progressively diminishes as toxemia increases, and believing that exogenous insulin is not neutralized by the toxemia, we thought that by giving graduated doses of insulin preceding the administration of dextrose the tolerance curves could be kept normal. This fact would lend weight to the explanation suggested.

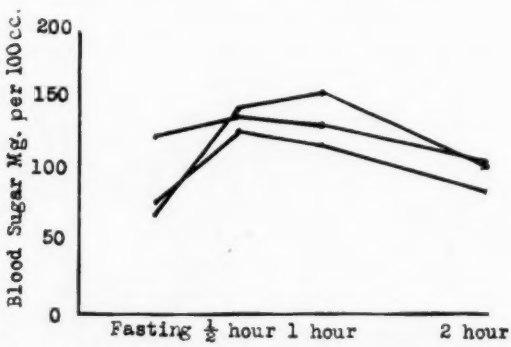

Chart 4.—Daily curves showing the tolerance for dextrose of rabbit E. The animal survived two days following the injection of 0.004 cc. of diphtheria toxin and was given 2 and 4 units on the first and second days of toxemia twenty minutes preceding the administration of 5 Gm. of dextrose (table 4).

TABLE 4.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit E* *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
0	0	73	146	159	104
24	2	85	136	120	94
48	4	125	143	133	105

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

Rabbits were used in the experiment. Food was withheld except after the tests and then removed within a few hours' time. Water was kept in the cages of the animals. Tolerance tests were made of all of the animals for a few days to establish controls. They then received injections of diphtheria toxin, the doses varying from 0.005 to 0.0025 cc. (minimum lethal dose, 0.02 cc.).[5] Arbitrarily following the first twenty-four hours of toxemia, 2 units of insulin was given twenty minutes before the dextrose was administered. This dose was again arbitrarily

5. The Eli Lilly Company furnished the diphtheria toxin and insulin used in this experiment.

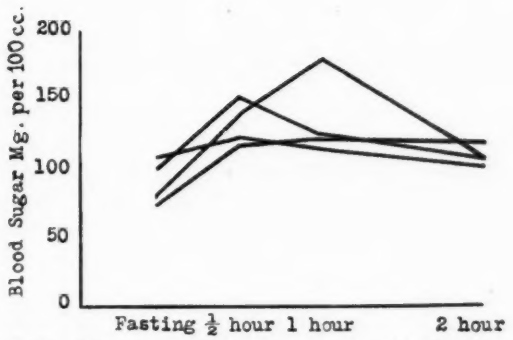

Chart 5.—Daily tolerance curves for dextrose of rabbit F. The animal was given 0.004 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 5).

TABLE 5.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit F* **

		Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
Hours of Toxemia	Units of Insulin	Fasting	30	60	120
0	0	88	143	182	108
24	2	102	151	128	106
48	4	111	125	118	103
72	6	83	118	125	121

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

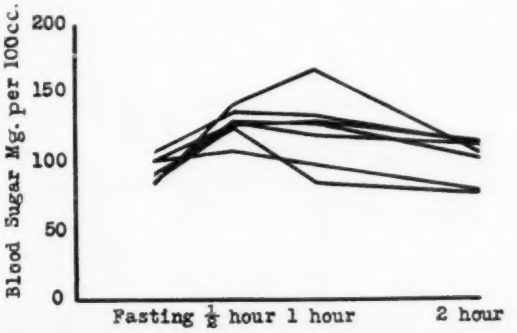

Chart 6.—Daily tolerance curves for dextrose of rabbit G. The animal received 0.005 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 6).

TABLE 6.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit G* **

		Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
Hours of Toxemia	Units of Insulin	Fasting	30	60	120
0	0	83	143	165	109
24	2	87	138	125	103
48	4	89	125	85	70
72	6	100	111	95	80
96	8	84	129	129	118
120	10	100	133	120	105
144	12	111	140	132	111

* This animal was given 0.005 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

increased 2 units daily and given each time twenty minutes preceding the dextrose. In view of previous tests performed on toxic but non-insulinized animals, no such controls were made in this series of observations. Table 1 and chart 1 are reproduced to illustrate the effect of toxemia on the tolerance for dextrose.

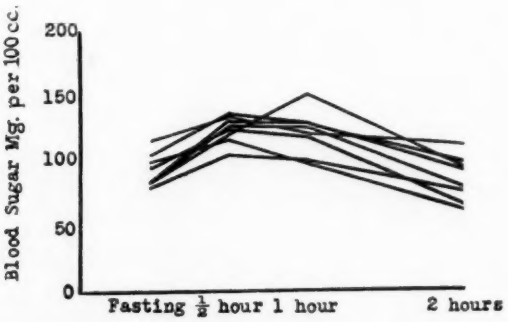

Chart 7.—Daily tolerance curves for dextrose of rabbit H. The animal received 0.0025 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 7).

TABLE 7.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit H* *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
0	0	89	123	154	92
24	2	90	133	129	85
48	4	83	111	100	80
72	6	95	129	120	70
96	8	100	118	100	67
120	10	111	143	133	93
144	12	89	131	131	100
168	14	118	138	125	118

* This animal was given 0.0025 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). Insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

The two groups studied were: (*a*) nontoxic rabbits that were given subcutaneously daily 2 unit increments of insulin twenty minutes before 5 Gm. of dextrose was administered by stomach tube; (*b*) toxic rabbits (they had received different dosages of diphtheria toxin, see the tables) that were given subcutaneously daily 2 unit increments of insulin twenty minutes before 5 Gm. of dextrose was administered by stomach tube. In both groups, the blood sugar after fasting was determined and insulin was injected; twenty minutes afterward dextrose was administered, and at thirty, sixty, ninety and one hundred and twenty minute intervals following the administration of dextrose, blood was collected from the

marginal ear veins for an estimation of the blood sugar. The blood sugar was estimated according to the Folin-Wu method. As stated earlier, table 1 and chart 1 are reproduced from a previous study to show in rabbits the effect of toxemia on the tolerance for dextrose without insulin. Table 2 and chart 2 are presented to show the dextrose tolerance curves for a nontoxic and noninsulinized rabbit and table 3

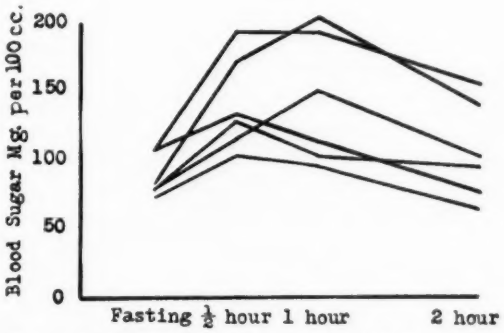

Chart 8.—Daily tolerance curves for dextrose of rabbit B. The animal received 0.004 cc. of diphtheria toxin. No insulin was injected on the first two days of toxemia. On the last three days, daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given (table 8).

TABLE 8.—*Results of Daily Tests of Tolerance for Dextrose on Rabbit B* *

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
0	0	80	118	152	107
24	0	83	174	211	143
48	0	111	191	191	167
72	6	111	138	118	83
96	8	83	133	108	95
120	10	77	105	95	69

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). No insulin was given the first two days of toxemia. During the last three days the insulin was injected each day twenty minutes before the 5 Gm. of dextrose was given.

and chart 3 to show the results of increasing doses of insulin in a nontoxic rabbit. It will be observed that the animal was unable to tolerate 6 units of insulin given twenty minutes before 5 Gm. of dextrose was administered; in fact, two hours after the administration of 4 units the animal showed symptoms suggestive of an impending convulsion.

Table 4 and chart 4 present the figures and curves for another rabbit, E, that received 0.004 cc. of diphtheria toxin, which apparently caused its death during the third day of toxemia. Table 5 and chart 5

contain figures and curves for rabbit F that lived into the fifth day of toxemia following 0.004 cc. of diphtheria toxin. Following the injection of 6 units of insulin on the fourth day of toxemia, the sugar tolerance curve was normal, or even might be called one of increased tolerance.

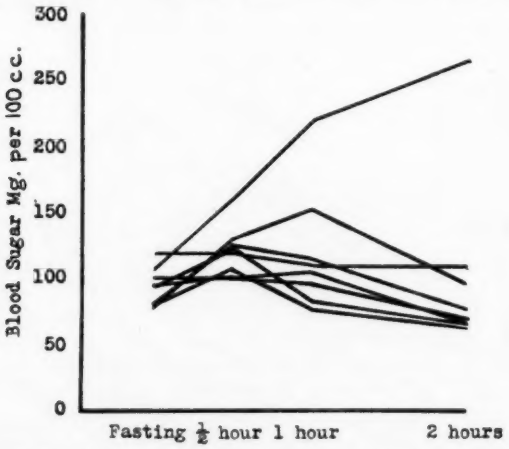

Chart 9.—Daily tolerance curves for dextrose on rabbit C. The animal received 0.004 cc. of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm. of dextrose was given, except on the sixth day. Note the high curve (table 9).

TABLE 9.—*Results of Daily Tests of Tolerance for Dextrose of Rabbit C* **

Hours of Toxemia	Units of Insulin	Blood Sugar, Mg. per 100 Cc.			
			After Dextrose, Min.		
		Fasting	30	60	120
0	0	80	133	153	93
24	2	83	129	120	80
48	4	80	111	77	65
72	6	91	125	85	67
96	8	100	100	95	70
120	10	90	100	105	67
144	0	111	167	222	267
168	12	118	118	111	111

* This animal was given 0.004 cc. of diphtheria toxin (minimum lethal dose, 0.02 cc.). On the sixth day of toxemia, insulin was omitted. On the other days, it was injected each time twenty minutes before the 5 Gm. of dextrose was given.

Rabbit G (table 6 and chart 6) was given 0.005 cc. of diphtheria toxin and survived six days, receiving on the last day 12 units of insulin twenty minutes before 5 Gm. of dextrose was administered. The tolerance curve was normal. In table 7 and chart 7 are the figures for rabbit H that received 0.0025 cc. of toxin, survived seven days and received on the last day 14 units of insulin. The dextrose tolerance curve was again normal.

Rabbit B (table 8 and chart 8) received 0.004 cc. of diphtheria toxin and lived five days. The first two days of toxemia no insulin was given preceding the administration of dextrose. The previously observed diminishing ability to remove dextrose from the blood may be observed. On the third day, however, 6 units of insulin was given as in the previous tests, then 8 and 10 units on the second and subsequent days of life, with resultant normal curves. Rabbit C (table 9 and chart 9), which received 0.004 cc. of diphtheria toxin, lived seven days. As a matter of interest, since the curves were like those for all other toxic rabbits, it was decided to omit insulin on the sixth day of toxemia. A rather sharply rising blood sugar curve was recorded, reaching a two hour level of 267 mg. On the following and last day of the rabbit's life, it was given 12 units of insulin before the dextrose was administered, and a practically level curve was recorded.

Section of the pancreas from toxic rabbit H, which survived seven days of toxemia, was studied by Dr. S. A. Wallace. The glandular epithelium was deeply stained, and the cytoplasm appeared swollen and granular in places. The islands of Langerhans varied in size and, in some of the islands, part of the cells were swollen, with a slightly granular cytoplasm. Many of the islands showed no definite change.

COMMENT

The explanation of these phenomena is difficult. That toxemia diminishes dextrose tolerance largely through thyrosuprarenal stimulation and glycogenolysis is difficult to accept. If such were the case, the blood sugar level after fasting would tend to increase from day to day, which it does not consistently do. It would likewise appear that there is something more than simply suppression of endogenous insulin. In fact, with such fairly large doses of insulin as the rabbits received in relation to the comparatively small quantity of dextrose administered, it would appear as though the animals were totally diabetic so far as exogenous insulin and administered dextrose are concerned. If our accepted ratio of 1 unit of insulin to 2 to 3 Gm. of dextrose is correct, and clinically and experimentally it is, then the only conclusion to be drawn from these observations is that toxemia interferes in some way with the function of insulin, whether the insulin is from an endogenous or an exogenous source. Further work is in progress that has been designed to aid in understanding the mechanism of the effect of toxemia on the tolerance for dextrose and the action of insulin.

SUMMARY

Reference is made to previous experiments showing the effect of toxemia on the tolerance for dextrose. In the present study, dextrose tolerance tests were performed on rabbits intoxicated with varying

doses of diphtheria toxin on successive days of their toxemia. Daily increased doses of insulin were injected subcutaneously twenty minutes before a constant quantity (5 Gm.) of dextrose was given. In this way, the tolerance curves consistently were kept within normal limits. As many as 12 or 14 units of insulin was given on the latter days of toxemia, with the result that the postprandial blood sugar readings continued to be within normal limits.

The only conclusion drawn is that toxemia in some way interferes with the function of insulin whether it is endogenous or exogenous in origin.

NOTE.—Mr. R. Rosenthal, senior medical student, assisted in these experiments.

531 Medical Arts Building.

SALMONELLA SUIPESTIFER BACTEREMIA WITH ACUTE ENDOCARDITIS

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AND
S. LEON ISRAEL, M.D.
PHILADELPHIA

Salmonella suipestifer is seldom encountered in the study of human disease, in spite of its close relationship with the typhoid and paratyphoid bacilli. For some time after knowledge of its association with the virus of hog cholera was recognized, bacteriologists waged a controversy as to its pathogenicity for man. In recent years, especially since the World War, there has been conclusive evidence of its specific relationship to some forms of human disease. During the war, there appeared reports from southern Europe and Asia Minor of epidemics of gastro-enteritis caused by a bacillus resembling that of paratyphoid fever, which was subsequently named the paratyphoid C bacillus. These epidemics were of brief duration and mild in character; especially noteworthy were those reported by MacAdam [1] in Mesopotamia and by Hirschfeld [2] in Serbia. A few years later, TenBroeck [3] and Andrewes and Neave [4] (working independently) identified this paratyphoid C bacillus as a member of the S. suipestifer family, and as giving reactions similar to those of the group I type. Shortly afterward, Savage and White,[5] using the Lister Institute's national collection of type cultures, recognized several cultures previously reported as paratyphoid C as really being S. suipestifer (footnote, table 1). They concluded that this organism was of low virulence and that it could produce human infection

From the Mount Sinai Hospital, Philadelphia.

Read before the Section on General Medicine, College of Physicians, Philadelphia, May 22, 1933.

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2. Hirschfeld, L.: A New Germ of Paratyphoid, Lancet **1**:296 (Feb. 22) 1919.

3. TenBroeck, C.: Bacilli of the Hog-Cholera Group (Bacillus Cholerae Suis) in Man, J. Exper. Med. **32**:33 (July) 1920.

4. Andrewes, F. W., and Neave, S.: Nature and Systematic Position of B. Paratyphosus C., Brit. J. Exper. Path. **2**:157 (Aug. 21) 1921.

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only under extraordinary circumstances. Following this bacteriologic pathfinding, many observers began to report epidemics of gastro-enteritis with the presence of S. suipestifer in the stools. Krumweide, Provost and Cooper [6] described an outbreak caused by eating tapioca pudding; Cowern [7] reported several cases among travelers coming from areas in which "intestinal grip" was prevalent; Schnitter [8] and Braun and Mündel [9] recorded an outbreak in 103 persons who attended a picnic; Savage and White [5] mentioned the infection of a family, apparently caused by cheese; Scott [10] reviewed five distinct epidemics over a period of a year in England, each caused by infected meat; Stewart and Litterer [11] reported an epidemic of 150 cases, supposedly from raw milk. All of these were from food infections, and acute gastro-enteritis was the usual clinical picture.

Following the recognition of the suipestifer enteritides, there began to appear sporadic reports of suipestifer bacteremias, accompanied by varied clinical syndromes, sometimes suggestive of typhoid fever and at other times of influenza of the "septic type." We have listed these reported cases of bacteremias chronologically (table 1), a total of 34; in each of these, the bacillus was found in the blood in pure culture with the exception of the case reported by Nabarro and White,[12] in which it was recovered from a synovial sac. We wish to add another case to this group of infections due to S. suipestifer and to report, at the same time, the appearance of endocarditis during the height of the bacteremia.

REPORT OF A CASE

T. M., a white boy, aged 4 years, was admitted to the hospital on March 15, 1933, having been ill for five days with fever, anorexia, vomiting, prostration and vague abdominal pain. The past medical and family histories were irrelevant. The

6. Krumweide, C.; Provost, D. J., and Cooper, G. M.: Studies on the Paratyphoid-Enteritides Group: Enteric Infection ("Food Poisoning") Due to Tapioca Pudding Contaminated with B. Cholerae Suis (B. Suipestifer), J. M. Research **43**:53 (Jan.-March) 1922.

7. Cowern, E. W.: Intestinal Influenza and B. Suipestifer, J. A. M. A. **86**:58 (Jan. 2) 1926.

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9. Braun, H., and Mündel, F.: Ueber den Erreger der Offenbacher Speiseeis-Epidemie, Klin. Wchnschr. **6**:1286 (July 2) 1927.

10. Scott, W. M.: The "Thompson" Type of Salmonella, J. Hyg. **25**:398 (Nov. 26) 1926.

11. Stewart, H. C., and Litterer, William: Outbreak of Gastro-Enteritis; Milk-Borne Epidemic of Dyersburg, Tenn., Caused by Salmonella Suipestifer, J. A. M. A. **89**:1584 (Nov. 5) 1927.

12. Nabarro, D.; White, P. B.; Dyke, S. C., and Scott, W. M.: Two Cases of Human Infection by American Hog-Cholera Bacillus, Lancet **2**:868 (Oct. 26) 1929.

illness started rather precipitately, with frontal headache and a sharp rise in temperature which remained constantly high (from 104 to 105.5 F.). There was a gross and irregular erythema over the trunk and arms for twenty-four hours; there was no sore throat. Persistent vomiting, marked prostration and a gradually

TABLE 1.—*Salmonella Suipestifer Bacteremias*

Year	Authors	Number of Cases: Adults	Number of Cases: Children	Ultimate Course: Recovered	Ultimate Course: Died	Symptomatology
1919	*MacAdam [1]	7	..	5	2	Mild typhoid fever and lobar pneumonia
1920	*Dudgeon and Urquhart: Lancet **2**: 15, 1920	..	1	1	..	Mild typhoid fever
1921	*Andrewes and Neave [4].....	1	..	1	..	Influenza with pleural effusion and pyuria
1922	MacKenzie: J. Roy. Army M. Corps **39**: 51, 1922	1	..	1	..	Infection of upper respiratory tract
1923	*Wordley: Brit. M. J. **2**: 105, 1923	..	1	1	..	Bronchopneumonia
1924	Duncan: J. Hyg. **22**: 402, 1924	1	..	1	..	Mild typhoid fever
1925	Kopp: Deutsche med. Wchnschr. **52**: 2156, 1926	1	..	1	..	Mild typhoid fever
1926	Shaw: J. Lab. & Clin. Med. **12**: 141, 1926	1	..	..	1	Severe bronchopneumonia
1927	†Hicks and Robertson: China M. J. **41**: 789, 1927	1	..	..	1	Typhoid fever
1928	Bullowa: M. Clin. North America **12**: 691, 1928	1	..	..	1	Severe bronchopneumonia
1929	Bauer and McClintock: J. Infect. Dis. **44**: 292, 1929	1	..	..	1	Mild typhoid fever
1929	Nabarro and White [13]....	..	1	1	..	Chronic arthritis
1929	Dyke and Scott [13].....	1	..	..	1	Mild typhoid fever
1930	Branham, Motyca and Devine: J. A. M. A. **94**: 1758 (May 31) 1931	1	..	..	1	Severe infection of upper respiratory tract
1931	TenBroeck, Li and Yu: J. Exper. Med. **53**: 307, 1931	4	1	3	2 (ad.)	Paratyphoid fever
1932	Rau: Ztschr. f. Kinderh. **52**: 510, 1932	..	1	..	1	Severe gastro-enteritis
1932	Kuttner and Zepp: Bull. Johns Hopkins Hosp. **51**: 373, 1932	..	7	7	..	Fever, abdominal pain and vomiting
1932	Haynes, quoted by Kuttner and Zepp	..	1	1	..	Paratyphoid fever
1933	Gouley and Israel.....	..	1	1	..	Mild typhoid fever and endocarditis
	Totals.....	21	14	24	11	(Only 1 of 11 deaths in a child)

* Cases reported as infections with paratyphoid C, but organism was later shown to be S. suipestifer.

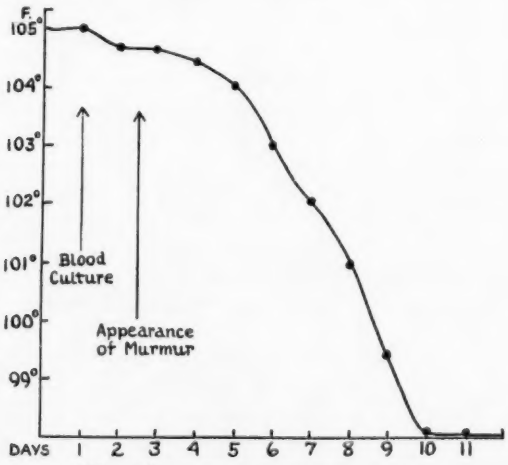
† Case reported as infection with paratyphoid C, but organism reacted like S. suipestifer.

increasing abdominal distention suggested the presence of primary peritonitis. On admission, the child's condition was extremely toxic. The temperature was 105 F., the pulse rate 140 and the respiratory rate 38. The heart and lungs exhibited no abnormalities, nor was there evidence of meningeal irritation; the abdomen was generally resistant and tender. The blood chemistry, the icterus index and the results of urinalyses and study of the cerebrospinal fluid were all within normal

limits; the Wassermann reaction was negative. The white blood cell count was 10,000, with 68 per cent polymorphonuclear cells.

Twenty-four hours after admission, the patient's abdomen was softer and he retained fluids administered orally. The hyperpyrexia persisted, as did the marked apathy; the leukocyte count fell to 7,600, with 65 per cent polymorphonuclear cells. A blood culture taken at this time became positive four days later. The spleen was now palpable.

Forty-eight hours after admission, a state of cardiac embarrassment developed, with marked tachycardia and cyanosis of the lips and finger tips. A sharp, rough, high pitched murmur was heard over the precordium, being most intense at the apex and transmitted to the back and axilla; at the same time, signs of pulmonary consolidation developed over the upper lobe of the right lung. The leukocyte count was 8,100, with 79 per cent polymorphonuclear cells.



The daily average temperature curve.

The Widal reaction was negative, and examination of the excreta for typhoid and paratyphoid bacilli gave negative results. A roentgenogram of the sinuses and chest revealed clouding of the ethmoid cells and incomplete consolidation of the upper lobe of the right lung. On the following day, the fourth day of hospitalization, a double aortic murmur appeared, and the pneumonic signs were less convincing. The temperature began to decline and, on the twelfth day of the illness, became normal (chart). The symptoms entirely disappeared, but the murmurs in both the mitral and the aortic area persisted. The patient left the hospital with a normal temperature on March 26, 1933. He has been under the care of one of us since that time, and there has been no recurrence of fever or any other untoward symptom; the mitral murmur persists, while the aortic murmur has lately disappeared.

The organism which grew in the blood culture broth, after four days of incubation, was a small, motile, gram-negative bacillus. With the aid of Dr. George Walter McCoy at the National Institute of Health

and of Dr. Carl TenBroeck of the Rockefeller Foundation, this bacillus was identified as S. suipestifer (probably group I variety). It formed acid in litmus milk, which became alkaline forty-eight hours later. Known suipestifer serum agglutinated it, as did the serum of the so-called paratyphoid C bacillus, and the fermentation reactions were typical of S. suipestifer.

The morphologic, cultural and serologic characteristics of S. suipestifer are those shown in table 2. In addition, it has a peculiar virulence for rabbit tissues, so that a culture may be transferred to the peritoneal cavity of a rabbit for further study. As a final diagnostic test, it is well to try to agglutinate the organism with some of the patient's serum some months after the original infection, at which time the titer should be high.

TABLE 2.—*Fermentation Reactions of Salmonella Suipestifer*

Acid and Gas	Acid	No Fermentation
Galactose	Xylose	Arabinose
Dextrose	Glycerol	Inosite
Levulose		Trehalose
Maltose		Dulcite *
Mannose		Lactose
Mannitol		
Rhamnose		

* Irregular and delayed acid formation occurred after twenty days.

COMMENT

The symptomatology of infection due to S. suipestifer readily divides itself into three groups: gastro-enteric, pulmonic and septic. A review of the 34 cases of bacteremia previously reported shows a predominance of adults and males. Age appears to be an important prognostic factor. There is an interesting difference in the morbidity and the mortality in the various age groups. The bacteremia apparently pursues a more violent course and has a higher mortality in adults; 21 of the 35 persons were adults and of these 12 died, a mortality of 57 per cent. There were 14 cases in children, of whom only 1 died, a mortality of 7 per cent.

The gastro-enteric form is the most common and often tends to mimic typhoid or paratyphoid fever. It ushers itself in rather suddenly with nausea and vomiting, abdominal discomfort and occasionally diarrhea. The abdominal discomfort is worthy of comment, inasmuch as two children of the reported series underwent fruitless laparotomies for apparent perforations of the appendix. In our case, the abdomen was tender and increasingly tense for the first few days, so that a diagnosis of primary peritonitis was entertained. The next most frequent syndrome, seen especially in children, is the so-called influenzal form, with vague myalgia, drowsiness, chills and hyperpyrexia without any localizing signs. This is often followed by pulmonary complications.

The highest mortality in the adult series obtained in cases with pneumonia. It is interesting to note that in the case reported here symptoms of all three groups were present: nausea, vomiting, abdominal pain, fleeting pneumonia and hyperpyrexia with drowsiness.

Cardiac changes have never been noted. No instance of endocarditis appears in the entire list of cases with suipestifer bacteremia; furthermore, it is a well known fact that endocarditis is a rare complication in the broad group of typhoid, paratyphoid and allied infections. That this endocardiac lesion was produced by the S. suipestifer may only be conjectured, but it is suggested by the fact that the murmurs appeared at the height of the bacteremia and persisted after it and by the fact that the child had never before presented evidence of valvular endocarditis. We are aware of the ease with which functional murmurs develop in children; the factor of cardiac dilatation had to be considered and probably did accentuate the murmurs. We believe at the present time, however, that the murmurs that developed at the height of the acute infection almost certainly represented organic lesions; the peculiar quality of the murmur, the fact that an aortic murmur was heard shortly after the appearance of the mitral murmur, and their persistence long after convalescence suggest that a definite endocarditis had developed. However, since this is the only case reported in which endocarditis developed during the course of suipestifer bacteremia, it is essential to think of other possible explanations, such as rheumatic fever. The presence of transient pneumonia coincidental with acute endocarditis in a child would be suggestive of a virulent rheumatic infection. If this were the case, S. suipestifer would have to be considered a secondary or, at best, a coincidental invader from the gastro-intestinal tract. However, the clinical course, aside from the endocardiac involvement, was not suggestive of a rheumatic infection, even though the features of acute rheumatism are remarkably protean. A review of the case makes a diagnosis of rheumatic endocarditis improbable in the light of the following factors:

1. The tendency to leukopenia, or at least the absence of leukocytosis, and the comparatively low polymorphonuclear cell count.

2. The sudden, explosive-like development of a murmur during the early stage of the illness and the very rough, high pitched quality of this murmur, in contrast to the usually insidious onset of systolic murmurs in the initial attack of acute rheumatic fever.

3. The absence of recurrent fever. It would appear from a study of the fever chart and the subsequent total absence of fever for a period of three months that we were dealing with a self-limited disease.

A remarkably constant phenomenon in an infection due to S. suipestifer is the low white blood cell count. Leukopenia was present in

almost every case in the series, and this is especially notable in view of the hyperpyrexia. The lowest count in the series was 4,800 and the highest 10,000. This, of course, is more or less expected to occur in bacteremia caused by any Salmonella, inasmuch as these organisms are members of the typhoid family.

The diagnosis of this disease is made partly by elimination of other possible infections, but is definitely established only by positive blood culture. Agglutination reactions with suipestifer should be borne in mind in any case of apparent typhoid or paratyphoid fever with a negative Widal reaction, but it must also be remembered that positive agglutination in high titer may not develop for many months. Moreover, a cross-agglutination between the patient's serum and paratyphoid bacillus B often occurs during the acute stage of infection caused by suipestifer, a fact that obscured the true identity of the latter organism until the characteristic carbohydrate fermentations were discovered and standardized. The positive blood culture and the carbohydrate reactions, therefore, lead to an accurate diagnosis; it is obvious that the matter of recognition of S. suipestifer requires a competent bacteriologist.

As to the endocarditis, we realize the limitations of a clinical report unsupported by pathologic evidence; the rarity of such a complication in infection with S. suipestifer prompted us to report its probable occurrence and in doing so to call to the attention of other observers, especially those who will be fortunate enough to see a larger number of cases, the possibility of cardiac involvement.

SUMMARY

1. A case of S. suipestifer bacteremia and accompanying endocarditis is described. This is the first report of the development of endocarditis as a complication of this bacteremia.

2. The frequency and symptomatology are discussed, with the citation of 34 cases previously reported.

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THE METABOLIC EXERCISE TOLERANCE TEST

A SIMPLIFIED METHOD

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In another communication,[1] a method was described for measuring the excess oxygen consumption during exercise, the oxygen debt and the time required for recovery. It was found that these measurements, particularly the excess oxygen consumption during exercise, were greater than normal in patients with organic heart disease and a history of some limitation of activity, even when no congestive heart failure was present. It was concluded that this test yields a useful objective quantitation of the cardiac capacity.

The method previously described involved the use of an extension arm on the usual Roth-Benedict basal metabolism machine, and the calculation of results from multiple slopes recorded on a long paper record made by pasting three of the standard basal metabolism sheets end to end. In the present communication we are describing a simplified method which, in addition to other advantages, facilitates the calculation of results.

METHOD

The present method differs from that previously described chiefly in the manner in which the excess oxygen consumption is recorded. The arrangement of the apparatus is shown diagrammatically in figure 1.

The spirometer is filled with oxygen from tank *A* and, if desired, the oxygen consumption during rest is determined or a basal metabolism test may be performed in the usual manner. When this is completed the clockwork drum is stopped and the spirometer is refilled from tank *A*. By means of a fine needle valve (*D*) oxygen is now introduced into the spirometer from tank *B*, through the flowmeter

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Aided by the Frederick K. Babson and the Max Pam Funds.

From the Metabolic and Cardiovascular Laboratories of the Department of Physiology, the Heart Station, and the Max Pam Unit, Michael Reese Hospital.

1. Katz, L. N.; Soskin, S.; Schutz, W. J.; Ackerman, W., and Plaut, J. L.: A "Metabolic Exercise Tolerance Test" for Patients with Cardiac Disease. A Feasible Method for Using the Excess Oxygen Consumption and the Recovery Time of Exercise as Criteria of the Cardiac Status, this issue, page 710.

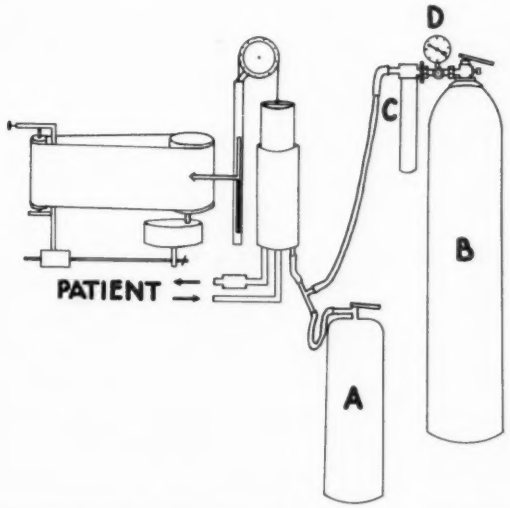

Fig. 1.—Diagrammatic representation of the apparatus for a simplified method of performing the test.

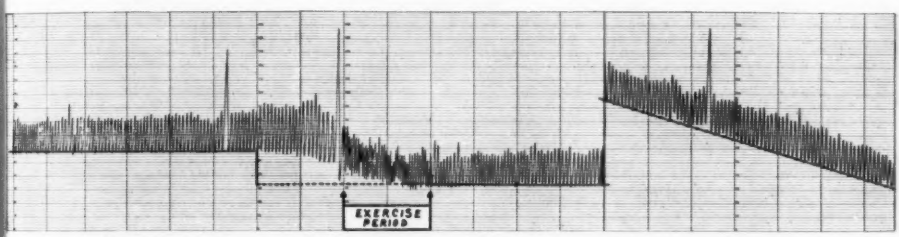

Fig. 2—A typical record of a woman, aged 20, whose weight was 121 pounds (54.9 Kg.), height 63 inches (190.5 cm.), body surface 155 square meters. The barometric pressure was 754 mm. of mercury and the average temperature 24 C. (75.2 F.). The exercise consisted in lifting two 2,625 Gm. weights through a distance of 37.5 cm. at a rate of 20 times a minute for two minutes. This represents approximately 80 kilogram-meters of work. Recovery time was two minutes. Excess oxygen consumption $= 58 - 34 = 24$ mm., or $= 24 \times 20.73 = 497.5$ cc. of oxygen. Corrected to standard temperature and barometric pressure the result is $497.5 \times .89 = 442.8$ cc. of oxygen. The excess oxygen consumption per kilogram-meter of work per square meter of body surface $= \frac{442.8}{80 \times 1.55} = 3.6$ cc.

(*C*) [2] at such a rate that the writing point continues to superimpose its record at the same constant expiratory level. The clockwork drum is now restarted and the record is observed for several minutes to insure the existence of an exact balance between the oxygen consumed by the resting patient and the oxygen introduced from tank *B*. Once this exact balance has been established, the adjustment of the needle valve is left unchanged for the duration of the test. Reading of the flowmeter offers an additional visual check on the constancy of the supply of oxygen at all times. With the oxygen flowing into the spirometer at a rate equal to the oxygen consumption during rest, the exercise is performed in the manner previously described, and the observations are continued until a new constant expiratory level is recorded.

The difference in height between the constant horizontal levels, before and after exercise, represents the excess oxygen consumption during the exercise. The time elapsing from the end of the exercise to the point at which the final horizontal level is first established represents the time required for recovery. The difference between the horizontal lines may be read directly from the ruled paper in millimeters and converted to cubic centimeters of oxygen by multiplying by the conversion factor 20.73.[3] The volume of gas is corrected to standard temperature and pressure in the usual manner. A typical record and calculation is shown in figure 2.

COMMENT

The present simplified method gives a more compact record than the method previously described. It permits a visual check on the steady state of the patient before the exercise and his return to the resting level after the exercise. The computation of the results is simpler and less subject to error, since it eliminates the periods of time necessary for refilling the spirometer and the necessity for drawing a slope for the irregular portion of the record during the period of exercise. Certain further possible simplifications of this method are suggested in the appendix.

The simplified method for the metabolic exercise tolerance test renders it hardly more difficult to perform than the ordinary basal metabolism test, once the equipment is assembled. In this form it is suitable for routine use in the clinical laboratory. The objective nature of the test, which eliminates the subjective influence of both patient and physician, makes it particularly suitable for the accumulation of data by different observers on large groups of persons. Such an application might be made in the classification of cardiac disability for insurance purposes.

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2. The flowmeter we have used is an oxygen metric flowmeter bottle, calibrated to a maximum of 650 cc., which may be obtained from the Foregger Company, Inc., New York.

3. The spirometer bell of the Roth-Benedict apparatus has a standard capacity of 20.73 cc. per millimeter of height.

SUMMARY

A simplified method is described for determining the excess oxygen consumption during exercise and time required for recovery by the metabolic exercise tolerance test.

APPENDIX

1. By using a base-line and time marker and a millimeter rule, it is possible to substitute plain kymograph paper for the ruled sheets for recording basal metabolism, thus avoiding the labor of pasting the latter together.

2. A slow moving drum may be used in conjunction with the modification just suggested to make the record more compact. This may obviate the necessity for building a kymograph extension.

3. If it is not desired to record the time required for recovery, it is possible to perform this test with the ordinary basal metabolism machine and paper. The preexercise and postexercise levels are recorded for a few minutes each, the clockwork drum being stopped during exercise and until the final horizontal seems to be established.

A "METABOLIC EXERCISE TOLERANCE TEST" FOR PATIENTS WITH CARDIAC DISEASE

A FEASIBLE METHOD FOR USING THE EXCESS OXYGEN CONSUMPTION AND THE RECOVERY TIME OF EXERCISE AS CRITERIA OF THE CARDIAC STATUS

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In accordance with the present trend of clinical medicine, there have been many attempts to devise methods for obtaining objective evidence concerning the functional condition of the heart in patients with cardiovascular disease. Such methods may be divided into two categories: (1) those which attempt to estimate the functional state of the heart at any given time, i. e., its ability to meet the routine demands of life, and (2) those designed to measure the cardiac reserve, i. e., the ability of the heart to meet emergency demands.

Most of the phenomena which have been observed under those methods have been the coincidental changes in the cardiovascular and respiratory systems, such as deviations from the normal in vital capacity, minute volume of respiration, venous pressure, minute volume of blood flow, circulation time, blood pressure and pulse rate. While these measurements within their limits of accuracy are of undoubted value in supplementing the impression gained from the history and physical examination in arriving at an estimate of the functional state of the heart, they are not necessarily related to the cardiac reserve. This objection has led to the development of various tests, which depend on the observation of the response of patients with heart disease to given

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Aided by the Emil and Fanny Wedeles, the Frederick K. Babson and the Max Pam Funds.

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stresses, such as muscular exercise,[1] anoxemia [2] and respiratory strain.[3] Despite the multiplicity of tests and modifications which have been proposed, not one has proved to be of sufficient practical value to gain general acceptance and use. A number of investigators have reported that the results of such tests in normal persons and in patients with heart disease do not parallel the obvious cardiac capacity as determined by the clinical examination.[4]

The problem is complicated by the fact that any test in which the patient is required to do work is influenced not only by the functional capacity of the heart but also by the condition of the patient as a whole. The factors of nervous tension, neuromuscular coordination and training, the condition of the respiratory system and similar conditions may far outweigh the factor of the capacity of the heart in the balance struck by the test. From a practical standpoint this situation is rather to be desired, since it is the ability of the patient and not merely of the heart to do work which is important from the clinical point of view. Nevertheless, these extracardiac factors are of extreme importance in determining the value of the criteria which one uses for estimating the cardiac reserve. It is not improbable that the failure of the various tests to justify their use rests on the inadequacy of the criteria which

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have been used in judging the results of such tests, rather than on any inappropriateness of the test itself.[5]

It has recently been shown that patients with organic heart disease require a greater amount of oxygen to perform a given amount of work than do normal persons (Bansi and Groscurth,[1a] Harris and Lipkin,[1d] Herbst[6] and Eppinger, Kisch and Schwarz[7]). This increase in the consumption of oxygen occurs largely during the period when the patient is recovering from the exercise, so that the oxygen debt is greater than normal and the recovery time is prolonged (Meakins and Long,[8] Campbell and Sale,[9] Nylin,[10] Bansi and Groscurth,[1a] Harris and Lipkin,[1d] Harrison and Pilcher[11] and Eppinger, Kisch and Schwarz[7]). This increased cost of work to the patient with cardiac disease cannot be ascribed to a greater consumption of oxygen by the heart alone, but must depend to a considerable extent on the extracardiac factors mentioned previously. Nevertheless, the measurement obtained is absolute, and need not be reinterpreted in terms of other relationships. It is well known, on the other hand, that the reaction of the heart rate, blood pressure and the like to exercise may show wide variations even in normal persons. Since the previous work indicated a real relationship between the cardiac reserve and the consumption of oxygen by the patient for a given exercise, it seemed worth while to attempt to devise a clinical functional test of cardiac capacity on this basis.

METHOD

The apparatus used consisted of the Benedict-Roth basal metabolism machine to which an extension arm had been added. The auxiliary drum, which could be fixed at any position along the extension arm, allowed for the use of a long paper record which was made by pasting three of the standard sheets for measuring basal metabolism end to end. The apparatus for the exercises, which was of the ordinary weight-and-pulley type, was fixed to a solid upright portable stand, which could be clamped to the foot of any hospital bed. Sturdy posts were fixed on the guide bars of the weights on the exerciser, so as to define sharply the distance through which the weights could be moved. An automatic counting device registered the number of lifts during a test. The ropes of the exercise machine were so adjusted

5. In the case of the minute volume of blood flow, which may be admitted to be an adequate criterion, its use in patients with heart disease is precluded because of the gross inaccuracies of our present methods of measurement in just such cases.

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10. Nylin, G.: Ztschr. f. klin. Med. **118**:584, 1931.

11. Harrison, T. R., and Pilcher, C.: J. Clin. Investigation **8**:291, 1930.

that the subject lying on his bed could lift the weights through the required range by flexing his arms without moving the rest of his body.

The subject to be tested was allowed to rest for half an hour on the experimental bed before the exercise was undertaken. At the end of the rest period, the mouthpiece and the clip for the nose were adjusted to the patient, and the consumption of oxygen while at rest was determined. No attempt was made to determine values for basal metabolism, but no test was performed sooner than three hours after the previous intake of food. After a period of eight minutes during which the metabolism while at rest was determined, the tank was refilled with oxygen while the patient was still attached to the machine, and the second period was begun. When a minute or two of this second period had elapsed, a metronome was started and the patient was signaled to begin the exercise concerning which he had previously been instructed. His consumption of oxygen was thus recorded continuously before, during and after the exercise, the oxygen tank being refilled when necessary. The test was continued for from fifteen to twenty minutes after the end of the exercise, by which time the consumption of oxygen had usually returned to the resting level.

In prescribing the kind and amount of exercise which would be suitable for the test, it seemed desirable to select that amount of work which would not be tiring to partially incapacitated patients, but which would at the same time cause a sufficient change in consumption of oxygen in subjects with a normal exercise tolerance. By the method of trial and error an acceptable exercise was found which consisted in lifting a 2,625 Gm. weight,[12] with each arm, through a distance of 37.5 cm., at a rate of 20 times a minute for two minutes. With arms fully extended and in semisupination the subject grasped the rope handles with the hands and, in time with the metronome, flexed his arms acutely at the elbows while the shoulder joints were comparatively without motion. When the patient was unable to continue for the full period of two minutes, and stopped before completing the usual exercise, the test was continued; the amount of work was calculated from the number of strokes recorded by the automatic counting device on the exerciser, and the results were calculated on this basis.

The total consumption of oxygen during the test is obtained by adding the consumption indicated by each separate slope. The oxygen consumed during the intervals between slopes (during the period of from ten to thirty seconds required for filling the spirometer) is obtained by projecting the slopes to cover these periods. Because of the irregularity of the slope during the exercise, which is probably accounted for by changes in the tidal and residual air in the subject, a line is drawn between the two points of the graphic record at the beginning and at the end of the exercise, the actual contour of this portion of the record being disregarded. The actual total consumption of oxygen during the test is compared with the consumption of oxygen for the same period of time calculated at the preexercise rate. The difference between these two amounts is taken to be the excess oxygen consumption of exercise, and is expressed as the excess oxygen in cubic centimeters per kilogram-meter of work per square meter of body surface. The recovery time is the time in minutes from the end of the exercise to the moment when the consumption of oxygen first returns to the preexercise level. A typical record of a test is shown in chart 1 and table 1.

12. No inference of precision as regards these weights is intended. The figure given happened to be the sum of the weights loaded on the exerciser when the best results were obtained. No allowance has been made for friction, etc.

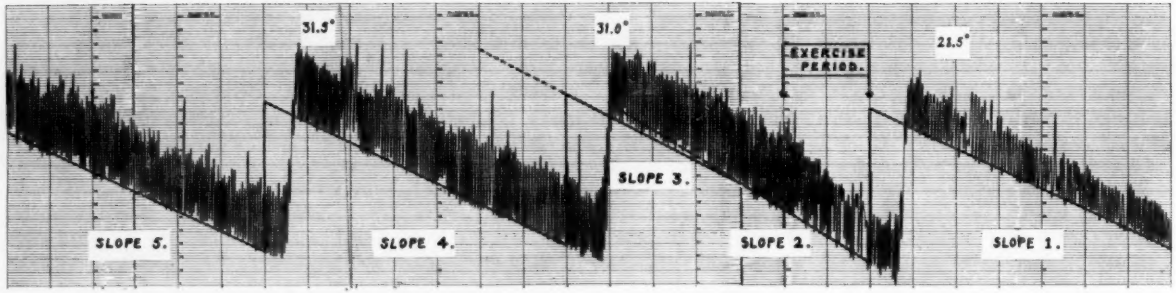

Chart 1.—Results of the test of one patient (J. B., table 3). The last food was taken four hours previous to the test.

The method of calculations is as follows:

Total actual consumption of oxygen (slopes 1 to 4) = 6,644 cc.

Consumption of oxygen for period of test (21 minutes), calculated at pre-exercise rate (slope 1) = $21 \times 296 = 6{,}216$ cc.

Excess consumption of oxygen of exercise = 6,644 — 6,216 = 428 cc.

Excess oxygen per kilogram-meter of work per square meter of body surface = $\frac{428}{80 \times 1.55} = 3.5$ cc.

Recovery time (duration of slopes 2, 3 and 4 minus the exercise period of 2 minutes) = 12 minutes.

Oxygen debt = total excess oxygen — excess oxygen during 2 minute exercise period = 428 — (389 — 296) × 2 = 242 cc.

Oxygen debt per kilogram-meter of work per square meter of body surface = $\frac{242}{80 \times 1.55} = 2$ cc.

TABLE 1.—*Record of Test of One Patient (J. B.)*

Slope	Chart Reading for Six Minutes, Calories per Hr.	Oxygen per Minute: From Standard Conversion Tables, Cc.	Oxygen per Minute: Corrected for Temperature and Barometric Pressure, Cc.	Actual Duration of Slope, Min.	Actual Oxygen Consumption, Cc.
1	90	310	296	7	2,072
2	119	412	389	3	1,167
3	99	342	321	4	1,284
4	93	322	303	7	2,121
5	90	310	292	6	

The apparatus required for this test is relatively inexpensive and is such as to be readily available in most institutions. Both the basal metabolism machine and the "exerciser" are mobile and can be wheeled from bed to bed in the hospital ward, thus obviating unnecessary disturbance of sick patients who are to be tested. The selection of exercise for the arms as opposed to exercise of the muscles of the legs was made to avoid large differences in training (Herbst[6]). As in the basal metabolism test, better results are obtained after the subject has become accustomed to the procedure. Although some subjects may have difficulty in following the metronome accurately, and may therefore not perform the exact number of lifts prescribed, the actual work done is indicated by the counting device on the exercising machine, and the calculations are made accordingly.

RESULTS

Two series of subjects were tested. One series consisted of twenty-six normal persons, thirteen men and thirteen women, interns, technicians and others, apparently in perfect health, on whom a total of forty-nine tests were made. The ages of these persons ranged from 19 to 33 years. The other series of subjects consisted of fourteen men and twelve women, patients attending the Adult Cardiac Clinic of the Michael Reese Hospital, on whom a total of forty-five

tests were made. The ages of these patients ranged from 13 to 36 years, with the exception of one patient who was 45 years old.

The subjects from the clinic were selected by one of us, on the basis of age and ability to cooperate, on the day of their visit to the clinic. However, no patient showing evidence of congestive heart failure was chosen. After agreeing to submit to the test, each patient went to the Max Pam Metabolism Unit, where the tests were performed. The patients were thus not specially prepared for the test, nor were the experimenters performing the test informed of the cardiac status of the patients they were testing.

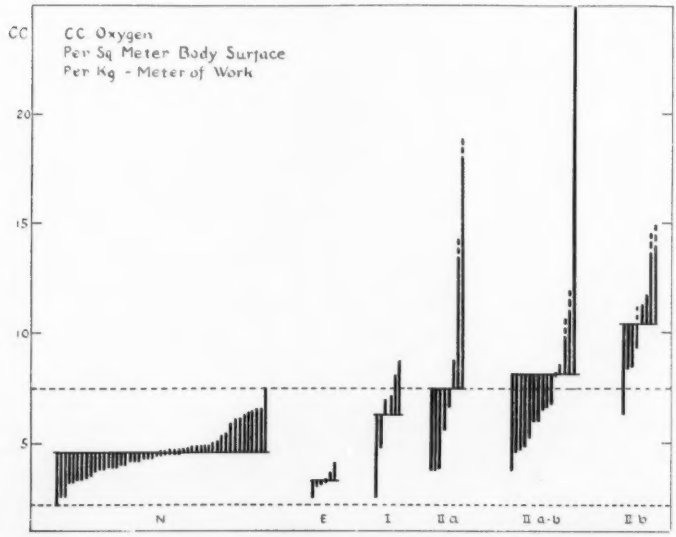

Chart 2.—The graphic comparison of the excess oxygen consumption of exercise in the normal subjects and in those with cardiac disease. In the normal group (*N*) and in each subgroup of the patients with cardiac disease (table 3, footnote *) the individual test values are drawn as vertical lines to the horizontal line, which is the mean value for the group. The horizontal broken lines represent the extreme range of the normal values. The dashes above certain of the vertical lines indicate that the tests represented by the lines were not continued to complete recovery from the exercise. The true mean value for groups containing such tests would therefore be higher than indicated.

Subsequent to the completion of this series of tests, the patients were asked to return to the clinic, at which time a clinical estimate of their cardiac status was made on the following basis: (1) history and physical examination at this time; (2) previous clinic and hospital records, and (3) information derived from social service records. The

TABLE 2.—*Results of Tests of Normal Subjects*

Name	Date, 1932	Age, Yrs.	Weight, Lbs.	Height, Inches	Body Surface, Sq.M.	Exercise: Strokes per Min.	Exercise: Duration, Min.	Exercise: Work,* Kg.-M.	Excess Oxygen per Kg.-M. of Work per Sq.M. of Body Surface	Recovery Time, Min.	Oxygen Debt per Kg.-M. of Work per Sq.M. of Body Surface
J. P. (M)	1/ 2	26	185	68½	1.95	30	2	120	4.6	6	2.7
	4/12	..	...	....	....	20	2	80	5.9	12½	4.2
	4/26	..	...	....	....	20	2	80	4.3	4½	2.6
	5/14	..	...	....	....	20	2	80	6.5	3	3.5
	5/24	..	...	....	....	20	2	80	6.4	4½	3.2
W. A. (M)	1/10	25	146	66½	1.75	30	2	120	4.6	6	2.3
	3/ 6	..	...	....	....	20	2	80	5.4	8½	3.9
	4/11	..	...	....	....	20	2	80	6.1	4½	3.4
	4/23	..	...	....	....	20	2	80	3.7	3	1.9
	5/22	..	...	....	....	20	2	80	3.2	4	1.4
W. S. (M)	3/22	25	155	70	1.85	20	2	80	3.4	1½	0.4
	4/11	..	...	....	....	20	2	80	3.9	3½	2.5
	4/22	..	...	....	....	20	2	80	3.8	3½	1.4
F. R. (F)	1/15	19	100	64½	1.45	30	2	120	4.2	6	1.6
	4/ 4	..	...	....	....	20	2	80	4.0	3	1.7
L. K. (F)	2/12	22	125	63	1.55	20	2	80	6.5	4	2.8
	4/ 6	..	...	....	....	20	2	80	5.1	2	1.5
R. S. (M)	2/15	23	160	73½	1.95	20	2	80	4.0	6	1.9
	3/ 5	..	...	....	....	30	2	120	4.3	3	2.4
V. E. (F)	2/ 8	33	115	66	1.55	20	2	80	4.6	5½	2.3
	4/26	..	...	....	....	20	2	80	4.9	6	3.6
D. Z. (M)	3/ 1	22	144	66½	1.75	20	2	80	2.5	5	1.0
	3/ 8	..	...	....	....	30	2	120	2.2	5	0.8
M. M. (F)	3/22	21	150	63	1.70	20	2	80	4.9	7	2.2
	3/23	..	...	....	....	20	2	80	4.2	5	1.2
C. G. (F)	3/22	21	97	60	1.35	20	2	80	4.9	4	2.3
	4/23	..	...	....	....	20	2	80	4.5	8	3.6
E. S. (F)	4/ 6	24	106	65	1.50	20	2	80	6.1	3	1.7
	4/18	..	...	....	....	20	2	80	7.5	8	2.9
B. T. (F)	4/ 6	22	168	66	1.85	20	2	80	3.5	3½	0.4
	4/12	..	...	....	....	20	2	80	3.9	2	1.3
H. P. (M)	4/ 7	27	160	68	1.85	20	2	80	4.7	4	2.2
	4/23	..	...	....	....	20	2	80	4.8	9	3.0
R. F. (M)	4/ 7	28	150	72	1.85	20	2	80	3.3	2½	1.0
	4/18	..	...	....	....	20	2	80	4.9	3	0.7
J. R. (F)	2/18	22	123	65½	1.60	20	2	80	4.3	8	1.4
	3/ 4	..	...	....	....	20	2	80	4.6	5½	1.5
K. J. (M)	12/29†	20	162	69½	1.90	30	2	120	4.5	4	1.2
M. R. (F)	1/19	20	121	63	1.55	30	2	120	5.3	5	2.9
G. J. (M)	3/18	28	140	66½	1.70	20	2	80	6.3	5	2.8
E. O. (F)	1/15	26	126	66	1.60	20	2	80	3.9	7	2.1
A. K. (M)	2/ 8	24	142	69½	1.80	30	2	120	3.3	5	1.6
R. S. (F)	4/ 5	21	115	62	1.50	20	2	80	3.8	5	0.9
G. C. (M)	5/17	25	179	70½	2.00	20	2	80	4.9	10	1.4
I. L. (M)	4/13	21	145	68½	1.80	20	2	80	5.0	2½	0.4
A. P. (M)	4/17	24	122	69½	1.65	20	2	80	3.2	3	1.0
C. B. (F)	12/19†	23	225	66	2.10	20	1	40	4.2	3	1.1
(obese)	1/12	..	...	....	....	30	2	120	6.3	4	4.5
V. O. (F) (obese)	1/ 5	20	230	68½	2.20	30	2	120	2.5	6	0.8
Average									4.6	5	

* The work per lift = 1.97 Kg.-M. For ease of calculation the value 2 has been used instead.
† 1931.

group of physicians making these estimates were not informed of the results of the so-called "metabolic exercise tolerance tests." From this clinical survey the patients were classified in the following five divisions (modified from the classification of the American Heart Association): class E, possible heart disease, with no apparent organic lesion; class I, organic heart disease, with no history of limitation of activity; class IIa, organic heart disease, with a history of slight limitation of activity; class IIa-b, organic heart disease, with a history of moderate limitation of activity, and class IIb, organic heart disease, with a history of marked limitation of activity. The data for each series of cases are summarized in tables 2 and 3, respectively, and the results of these series are compared in charts 2 and 3.

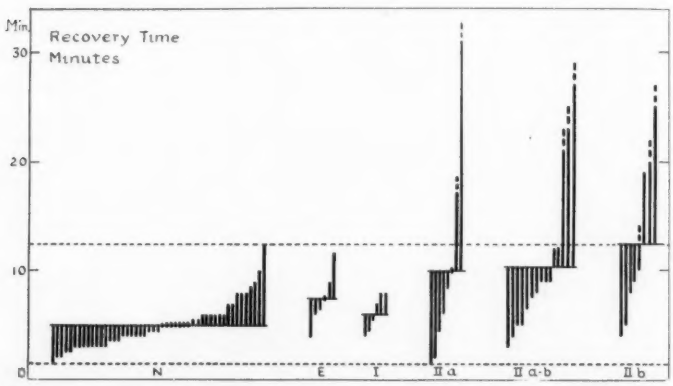

Chart 3.—The graphic comparison of the recovery time after exercise in the normal subjects and in those with cardiac disease. The conventions are similar to those in chart 2.

COMMENT

In order to arrive at comparable figures for different persons, the excess oxygen of exercise has been calculated as the excess oxygen per kilogram-meter of work per square meter of body surface. These values, for the normal persons tested, show a surprisingly normal distribution curve with a mean value of 4.6 and a range of from 2.2 to 7.5 (chart 2). The recovery time for the same group shows a similar distribution (chart 3). The ranges for both excess oxygen and recovery time are not much greater for the entire group of normal subjects than for a number of tests performed on a single normal person at intervals (J. P. and W. A., table 2).

The values for excess oxygen consumption and recovery time for class E, patients with no apparent organic heart lesions, fall well within

the normal range (charts 2 and 3). The results of these tests serve as an additional control and obviate the possibility of differences between our normal subjects and those with cardiac disease as to environment, social stratum, personal hygiene and other factors.

The excess oxygen consumption and recovery time in the groups of patients with organic heart disease show mean values which are progressively higher than the mean value of the normal subjects as one passes from the group with no limitation of activity (class I) to the group with marked limitation of activity (class IIb). There is also a progressive tendency for more of the individual values in these successive groups to be outside the normal range. It is apparent that the recovery time does not show as close a relationship to the clinical classification as does the excess oxygen consumption. However, there can be no question about the striking difference between classes I and IIb as regards both of these measurements. It is surprising that there should be such distinct graded differences in the excess oxygen consumption of classes IIa, IIa-b and IIb, considering the manner in which these groups were established. The results show that, even in the absence of congestive heart failure, patients with organic heart disease have an increased oxygen requirement and recovery time, for a given amount of work, which are roughly proportional to the history of limitation of activity.

The figures for oxygen debt in both the normal subjects and in those with cardiac disease roughly parallel the figures for excess oxygen consumption. The poorer relationship of the former to the clinical classification, however, renders it less suitable than the latter as a measure of the test. This is probably accounted for by the mild and brief nature of the exercise employed in the present series; during such a short period, the variation in different patients in the time required for adjustment to the effort may significantly affect the distribution of the excess oxygen consumption between the periods of exercise and recovery.

Our results are in agreement with those in the literature cited earlier in the article. However, a few observers claim to have found no increase in excess oxygen consumption of exercise even in patients with congestive heart failure.[13] Such results are difficult to reconcile with our own. An examination of their protocols, however, suggests that their findings may be influenced by the fact that they did not observe their patients for a sufficiently long period following the

13. Peabody, F. W., and Sturges, C. C.: Clinical Studies on the Respiration, Arch. Int. Med. **29**:277 (March) 1922. Alt, H. L.; Walker, G. L., and Smith, W. C.: The Cardiac Output in Heart Disease, Arch. Int. Med. **45**:958 (June) 1930. Harrison and Pilcher.[11]

TABLE 3.—*Results of Tests of Patients with Cardiac Disease* *

Name	Date, 1932	Age, Years	Weight, Pounds	Height, Inches	Body Surface, Sq.M.	Exercise: Strokes, per M.	Exercise: Duration, Min.	Exercise: Work, Kg.-M.	Excess Oxygen per Kg.-M. of Work per Sq.M. of Body Surface	Recovery Time, Min.	Oxygen Debt per Kg.-M. of Work per Sq.M. of Body Surface	Class	Heart Rhythm	Cardiac Enlargement	Valve Involvement	Etiology	Comment
J. B. (M)	4/27	17	115	64	1.55	20	2	80	3.5	12	2.0	E	SR	NE	...	...	Systolic murmur at apex
S. S. (F)	3/30	16½	102	63	1.45	20	2	80	4.2	9	2.8	E	SR	NE	...	NC	
	4/13	..	...	..	....	20	2	80	3.3	6	1.1						
J. R. (M)	3/23	17	138	72	1.80	20	2	80	3.0	6½	1.4	E	SR	NE	...	...	Systolic murmur at apex
A. G. (M)	3/23	14	126	66	1.65	20	2	80	3.7	7½	2.4	E	SR	NE	...	...	Systolic murmur at apex
O. B. (F)	2/ 3	15½	122	62	1.55	20	2	80	2.5	4	1.5	E	ST	NE	...	...	Palpable thyroid roughened first at apex
Average									3.3	7.5							
S. K. (F)	4/20	15	130	63	1.60	20	2	80	7.2	4½	5.4	I	SR	SE	...	...	Systolic over pulmonic area
B. V. (M)	4/20	18	123	66	1.60	20	2	80	7.0	7	3.0	I	SR	SE	...	CH	Systolic over base and sternum
L. D. (F)	3/ 9	25	140	67	1.70	20	2	80	2.5	4	1.4	I	SR	SE	DM	R	
S. G. (F)	2/24	20	132	61½	1.60	20	2	80	4.8	8	1.7	I	SR	SE	DM	R	
H. G. (M)	2/10	15	122	68	1.65	20	2	80	8.2	8	4.0	I	ST	SE	DM	R	Has fever on occasion
	4/27	..	...	..	....	20	2	80	8.9	5½	3.6						
Average									6.4	6.0							
L. G. (F)	3/23	17	115	61	1.50	20	2	80	5.1	14	2.4	IIa	SR	ME	DM	R	
	4/30	..	...	..	....	20	2	80	6.2	7	3.5	..	...	...	DA		
A. A. (F)	3/ 9	24	80	61	1.35	20	2	80	13.5+	17(NR)	10.2+	IIa	SR	SE	DM	R	
	5/ 2	..	...	..	....	20	2	80	8.8	8½	4.3						
O. K. (M)	5/13	14½	76	58	1.20	20	1½	60	18.1+	31(NR)	13.2+	IIa	ST	SE	DM	R	Hyperthyroidism
W. G. (M)	4/20	18	141	67	1.70	20	2	80	3.6	2	0.1	IIa	SR	ME	DM	R	
	4/30	..	...	..	....	20	2	80	5.6	1½	0.1	..	...	...	AI		

O. M. (M)	2/17	35	157	68½	1.85	20	2	80	6.6	10	3.9	IIa	SR	SE	DM	R	
H. K. (M)	2/10	16	131	70½	1.75	20	2	80	3.7	6	1.8	IIa	SR	ME	DM	R	
	4/30	..	...	..	....	20	2	80	3.6	4⅛	0.6						
Average									7.5+	10.0+							
H. L. (F)	4/ 6	16	112	63½	1.50	20	2	80	8.6	9	5.5	IIa-b	SR	ME	DM	R	
	4/13	..	...	..	....	20	2	80	11.1+	23(NR)	8.4+						
	4/30	..	...	..	....	20	2	80	6.0	12	3.1						
	5/28	..	...	..	....	20	2	80	4.7	9	1.9						
D. S. (F)	3/17	14	87½	60	1.30	20	2	80	8.2	5½	6.9	IIa-b	SR	TE	DM	R	
	4/30	..	...	..	....	20	1¾	70	9.8+	21(NR)	8.7+						
J. G. (M)	2/ 3	18	145	69	1.80	20	2	80	6.0	3	3.1	IIa-b	SR	ME	DM	R	Subacute bacterial endocarditis
	5/ 2	..	...	..	....	20	2	80	6.8	12	3.8	..	Ex	...	DA	...	Quiescent
	6/27	..	...	..	....	20	2	80	5.2	8	2.4						
C. W. (M)	2/17	45	151	68	1.80	20	2	80	4.8	4	2.4	IIa-b	AF	SE	DM	R	(Dead)
	5/11	..	...	..	....	20	2	80	3.7	5	1.8						
L. S. (F)	3/16	13	120	62	1.55	20	2	80	6.5	9	5.0	IIa-b	SR	SE	DM	R	
	5/14	..	...	..	....	20	2	80	6.6	5	3.0						
M. B. (F)	3/16	29	138	67	1.70	20	2	80	4.6	7½	1.6	IIa-b	SR	SE	DM	R	
	4/29	..	...	..	....	20	2	80	30.5+	27(NR)	25.3+						
Average									8.2+	10.5+							
B. S. (M)	2/18	16	123	60½	1.50	20	2	80	11.7	8	7.8	IIb	PT	ME	DM	R	(Dead)
	4/27	..	...	..	....	20	2	80	6.3	4	4.6	..	...	...	AI		
	5/18	..	...	..	....	20	2	80	8.5	5	6.7						
	5/28	..	...	..	....	20	2	80	8.4	9	6.1						
	6/25	..	...	..	....	20	2	80	11.3	19	8.6						
E. L. (M)	2/18	15	129	69	1.70	20	2	80	14.0+	20(NR)	11.2+	IIb	SR	ME	DM	R	
B. W. (F)	2/24	36	107	65	1.50	20	1⅛	72	9.4+	25(NR)	6.5+	IIb	AF	TE	DM	R	(Dead)
A. M. (M)	4/13	23	125	67	1.65	20	2	80	13.7+	10(NR)†	12.8+	IIb	AF	ME	DM	R	
Average									10.4+	12.5+							

* NR indicates that patient had not returned to preexercise metabolic rate; E indicates possible heart disease, no apparent organic lesion; I, organic heart disease, no history of limitation of activity; IIa, organic heart disease, history of slight limitation of activity; IIa-b, organic heart disease, history of moderate limitation of activity; IIb, organic heart disease, history of marked limitation of activity; SR, sinus rhythm; ST, sinus tachycardia; AF, auricular fibrillation; Ex, extrasystoles; PT, paroxysmal tachycardia; NE, no cardiac enlargement; SE, slight cardiac enlargement (apex outside nipple); ME, moderate cardiac enlargement (apex up to anterior axillary line); TE, Marked cardiac enlargement (apex up to midaxillary line); DM, double mitral (stenosis and insufficiency); DA, double aortic (stenosis and insufficiency); AI, aortic insufficiency; R, rheumatic heart disease; CH, congenital heart disease; NC, neurocirculatory asthenia.

† Experiment was stopped at this time, as patient was dyspneic.

exercise. It can be seen that some of our patients without congestive heart failure did not fully recover from the exercise within twenty minutes. The rate of excess oxygen consumption at this time may be small; nevertheless, over a period of many minutes, it may significantly affect the total excess oxygen consumed.

The variation in the results of our test on the same normal subject at different times has already been pointed out. The variability is even greater in a patient with organic heart disease and a history of limitation of activity (A. A., H. L. and M. B., table 3). This is not surprising in view of the clinical history of fluctuations in well-being in such patients. This probably explains the presence of tests within the normal range in the groups of persons with cardiac disease with limitation of activity; the clinical classification is based on the history of the maximum limitations and not so much on the condition of the patient at the time of a particular examination. In view of the narrow range we have obtained in normal subjects the wider range in patients with cardiac disease does not impute the adequacy of the test we have employed; but it does indicate that we have been dealing with real variations in the individual. A series of tests on patients developing and recovering from congestive heart failure and on patients with reactivation of rheumatic infection is in progress, in order more exactly to correlate the results of our test with the condition of the patient at the time of the test.

On the basis of our results, we believe that this test holds promise of deserving a definite place in the armamentarium of the clinic for cardiac disease. Although the test shows only an approximate parallelism with the classification of the American Heart Association, the differences found may depend on: (1) the objective nature of this test as opposed to the clinical classification, which may be influenced by the subjective states of both physician and patient, and (2) the fact that the test indicates the condition of the patient at the time of observation, while the clinical classification is based on the history of recent maximum disability of the patient.

It is obvious that no test can in itself determine the prognosis and treatment of a given patient. We believe, however, that the metabolic exercise tolerance test may be a valuable adjunct in determining these important elements in the management of cardiac disease.

SUMMARY

1. A relatively simple method has been devised for measuring the excess oxygen consumption in exercise, the oxygen debt and the recovery time. This metabolic exercise tolerance test has been applied to a group

of normal persons and to a group of patients attending the clinic for cardiac disease, and the results have been compared.

2. It was found that these measurements, particularly of the excess oxygen consumption of exercise, were greater than normal in patients with organic heart disease and with a history of some limitation of activity, even when no congestive heart failure was present. When these patients are classified into subgroups, according to the history of the degree of limitation of activity, the measurements become progressively greater as one passes from the group with no limitation of activity to the group with marked limitation.

3. It is concluded that this test, which yields an objective quantitation of the cardiac capacity of a patient at the time of examination, merits further consideration as an adjunct in the study of cardiac disease.

CONGESTIVE HEART FAILURE

XIX. REFLEX STIMULATION OF RESPIRATION AS THE CAUSE OF EVENING DYSPNEA

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In the preceding paper of the present series [1] it was pointed out that the term nocturnal dyspnea includes three different clinical syndromes, which may or may not coexist in the same patient. For the first syndrome the term "evening dyspnea" was suggested. A patient suffering from this type of respiratory distress is relatively (or entirely) free from dyspnea in the morning when he awakens, but as the day passes increasing respiratory discomfort gradually develops, reaches its maximum in the evening hours and may prevent the sufferer from going to sleep. At length, either with or without the use of sedatives, he finally sleeps and in the morning awakens with less or no respiratory discomfort, only to undergo a repetition of the same cycle. It should be noted that dyspnea of this type is not paroxysmal, but that the discomfort sets in gradually.[2]

The present paper is concerned with an attempt to elucidate the factors concerned in the production of this syndrome. For this purpose analyses of the arterial blood, measurements of pulse rate, blood pressure, oxygen consumption, ventilation and vital capacity were made in the morning and in the evening. Except when otherwise stated, the methods used were those which have been applied in the preceding studies of the series.

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1. Harrison, W. G., Jr.; Calhoun, J. A., and Harrison, T. R.: Congestive Heart Failure: XVIII. Clinical Types of Nocturnal Dyspnea, Arch. Int. Med. **53**:561 (April) 1934.

2. In this description we do not refer to orthopnea. Ambulatory patients may be free from dyspnea during the day—provided they are not too active—and then on getting into bed become short of breath and have to sit up. In the majority of patients with cardiac dyspnea of any type, orthopnea is also present. The term "evening dyspnea" as used in this paper refers to respiratory distress which is worse in the latter part of the day even though the patient remains in bed in the same position throughout the day.

OBSERVATIONS ON PATIENTS WITH CONGESTIVE HEART FAILURE

1. *Comparison of Morning and Evening Values for the Blood Gases and Hydrogen Ion Concentration.*—To determine whether evening dyspnea was due to alterations in the acidity and allied functions of the blood, observations were made on three patients in the morning before breakfast and in the late afternoon or evening, all the samples of blood being drawn at least four hours after the preceding meal. Blood was obtained from the brachial artery. Analyses for oxygen and carbon dioxide were done on the Van Slyke-Neill [3] blood gas apparatus, and hydrogen ion concentrations were determined by Cullen's [4] colorimetric method. Carbon dioxide tensions were calculated from the Hasselbach formula, the value of pK′ being assumed to be 6.1.

The data are shown in table 1. Eight comparisons between morning and evening values were made on the three patients, each of whom complained of more dyspnea in the latter part of the day. In six instances the oxygen capacity was slightly greater in the morning than in the evening. The opposite relationship was observed once, and no difference was noted once. The arterial oxygen saturation was, on the contrary, higher in the afternoon in seven of eight comparisons. The changes were not striking, but were well beyond the error of the methods used.

The carbon dioxide content of the arterial serum showed no constant alteration, being on an average slightly lower in the afternoon than in the morning. The values for p_H were variable. Two of the patients had more alkaline blood in the evening than in the morning, a finding which is similar to that reported by Cullen and Earle [5] in normal persons. The third patient's blood exhibited wide but inconstant fluctuations in reaction. On an average in all observations the blood was slightly more alkaline in the evening than in the morning. The carbon dioxide tension of the blood drawn in the evening was greater twice, the same once and lower five times than the value obtained in the morning. The mean carbon dioxide pressure was slightly greater in the samples drawn in the morning.

These observations seem to indicate clearly that the tendency toward dyspnea in the latter part of the day cannot be attributed to changes in the acid-base condition of the blood. Although there was considerable variation in the individual observations, the average alterations in the

3. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

4. Cullen, G. E.: Studies of Acidosis: XIX. The Colorimetric Determination of the Hydrogen Ion Concentration of Blood Plasma, J. Biol. Chem. **52**:501, 1922.

5. Cullen, G. E., and Earle, I. P.: Studies of the Acid-Base Condition of the Blood: II. Physiological Changes in Acid-Base Condition Throughout the Day, J. Biol. Chem. **83**:545, 1929.

TABLE 1.—*Diurnal Variations in Gases and in Hydrogen Ion Concentration of Arterial Blood*

Subject	Clinical Data	Date	Oxygen Content: Volumes per Cent		Oxygen Capacity: Volumes per Cent		Oxygen Saturation, per Cent		Carbon Dioxide Content of Serum: Volumes per Cent		p_H of Serum		Carbon Dioxide Pressure of Serum, Mm. of Mercury	
			Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
E. G.	Syphilitic aortic insufficiency	3/ 8/32	15.7	15.5	17.4	16.9	90.2	91.8	67.8	61.5	7.46	7.37	42.2	46.7
		3/ 9/32	16.1	16.0	17.3	16.6	93.0	96.4	63.8	64.2	7.40	7.29	45.3	58.0
		3/10/32	15.9	16.2	17.5	16.6	90.9	97.6	65.2	63.4	7.27	7.26	61.4	61.4
		3/11/32	15.7	14.5	17.5	15.2	89.8	95.6	63.3	61.6	7.28	7.43	59.5	41.0
P. F.	Syphilitic aortic insufficiency	3/29/32	17.2	17.0	18.9	18.5	90.6	92.0	51.7	51.7	7.38	7.41	38.3	36.0
		3/30/32	17.9	17.5	19.0	19.6	94.2	89.4	52.0	49.4	7.40	7.42	36.9	33.6
W. O.	Hypertension	3/28/32	....	17.6	....	17.6	....	100.0	....	54.1	....	7.46	....	33.8
		3/29/32	16.8	17.1	17.6	17.8	95.5	96.2	55.7	58.0	7.41	7.47	38.8	35.4
		3/30/32	16.9	....	18.6	....	91.0	....	55.1	....	7.39	....	40.0	....
Average values.....			16.5	16.4	18.0	17.4	91.9	94.9	59.5	58.0	7.37	7.39	45.3	43.3

blood in the evening (higher oxygen saturation, lower carbon dioxide pressure and greater alkalinity) might be regarded as effects of dyspnea, but could not conceivably have been its cause.

2. *Comparison of Morning and Evening Values of Circulatory and Respiratory Functions.*—In a further attempt to gain an insight into the mechanism of the diurnal variations in the degree of dyspnea additional observations were made. Pulse rate, blood pressure, respiratory rate, ventilation, vital capacity and oxygen consumption were measured in the morning before breakfast and at night. Blood pressures were measured with a mercury manometer. In some of the patients with aortic insufficiency the diastolic pressure could not be accurately determined and hence was not recorded. Oxygen consumption was recorded graphically with a Benedict-Roth spirometer. In some instances ventilation and respiratory rate were calculated from the tracing; in other observations the expired air was collected in a Tissot spirometer, and the respirations were counted with a stop watch. Vital capacity was determined in two patients by the usual spirometer method and in the remaining subjects by the technic described in a previous paper in the present series.[6] The latter method is not well adapted to extremely dyspneic subjects, but is more accurate for patients who are not excessively short of breath and who breathe smoothly.

The patients were kept in bed, and no therapy was given during the day except digitalis, the dosage of which was maintained at a constant level of 0.2 Gm. daily. After the observations in the evening sedatives were administered if necessary. When the patient did not sleep, the observations made on the following day were discarded. Likewise, when a patient's clinical state necessitated any therapeutic procedure, such as the administration of morphine, diuretics or venesection, the observations made on that day were omitted from consideration. Such omissions were obviously necessary, for the study was primarily concerned with determining why the clinical state tends spontaneously to become worse later in the day, and hence any procedure which made the patient's dyspnea less in the evening than in the morning invalidated the results.

Three groups of persons were studied. Each group consisted of four men and two women. Comparisons of the measurements obtained in the morning and in the evening were made on six patients with congestive heart failure and dyspnea which was greater in the evening than in the morning. Patients with severe dyspnea were not studied,

6. Calhoun, J. A.; Cullen, G. E.; Harrison, T. R.; Wilkins, W. E., and Tims, M. M.: Studies in Congestive Heart Failure: XIV. Orthopnea: Its Relation to Ventilation, Vital Capacity, Oxygen Saturation and Acid-Base Condition of Arterial and Jugular Blood, J. Clin. Investigation **10**:833, 1931.

TABLE 2.—*A Comparison of Morning and Evening Measurements of Circulatory and Respiratory Functions in Patients with Evening Dyspnea*

Subject	Sex	Chief Diagnosis	Date	Cardiac Rate per Minute		Systolic Blood Pressure, Mm. of Mercury		Diastolic Blood Pressure, Mm. of Mercury		Respiratory Rate per Minute		Ventilation per Minute, Liters		Mean Tidal Air, Cc.		Oxygen Consumption per Minute, Cc.		Vital Capacity, Liters	
				A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.
R. S.	M	Arteriosclerosis	12/12/31	96	87	144	156	90	86	15	21	7.16	9.62	478	458	285	287	2.61	2.20
E. G.	M	Syphilitic aortic insufficiency	12/18/31	104	96	214	186	70	74	18	18	12.20	11.44	678	636	258	287	2.43	2.13
			12/19/31	...	...	...	...	..	..	17	19	....	....	...	...	...	...	2.57	2.40
			12/21/31	90	87	170	180	70	80	20	31	10.40	12.00	521	388	...	...	2.97	2.57
			12/29/31	92	94	176	162	78	90	20	15	8.18	6.43	409	428	276	304	3.01	2.57
			1/ 3/32	88	88	164	174	80	80	18	20	6.70	9.12	372	456	258	300	2.58	2.78
M. G.	F	Hypertension	12/10/31	100	104	194	166	84	80	29	31	8.95	10.35	309	334	276	287	1.62	1.30
			12/11/31	108	102	168	182	85	80	20	26	8.29	9.20	414	354	261	285	1.62	1.57
			12/11/31	84	99	144	170	70	80	20	26	7.01	9.62	350	343	251	278	1.88	1.82
			12/16/31	84	76	140	134	60	64	22	27	7.43	10.20	338	372	266	265	1.99	1.77
			12/17/31	72	96	134	170	68	60	24	25	9.10	11.13	379	445	231	300	1.91	1.84
S. U.	F	Rheumatic aortic insufficiency	12/15/31	72	66	124	122	80	68	17	19	7.67	8.88	452	465	253	279	3.44	3.11
			12/16/31	72	67	136	128	80	76	17	18	7.43	8.64	437—	480	256	277	3.28	3.21
A. C.	M	Syphilitic aortic insufficiency	1/ 5/31	60	47	156	160	..	..	..	..	....	....	...	...	...	...	2.78	2.69
J. D.	M	Syphilitic aortic insufficiency	10/15/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.20	2.15
			10/16/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.30	2.20
			10/17/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.30	2.10
			10/18/31	...	...	...	...	..	..	.	..	....	....	...	...	...	...	2.25	2.15
E. G.	M	Syphilitic aortic insufficiency	10/15/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.85	2.49
			10/16/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.65	2.40
			10/17/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2,65	2.50
			10/18/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	2.75	2.60
			10/19/31	...	...	...	...	..	..	..	..	....	....	...	...	...	...	3.00	2.70

as respiratory measurements may cause such patients considerable discomfort and also are rather unreliable. Four of the six patients had been studied in the past and were well accustomed to the various procedures involved.

For purposes of control, observations were made on six patients without cardiac disease and on six subjects with cardiac lesions but without dyspnea.

The data obtained from the patients with evening dyspnea are shown in table 2. Constant differences in pulse rate and in the systolic and diastolic blood pressures were not found, these functions being greater in the morning in some observations and of larger magnitude in the evening in other observations. The average values for these functions were practically identical, as shown in table 3. It is therefore evident that evening dyspnea cannot in general be ascribed to tachycardia developing during the day and likewise is not dependent on increased cardiac work because of a rising blood pressure in the evening hours.

Unlike the circulatory functions, the respiratory factors exhibited rather definite alterations during the day. In one of thirteen comparisons the rate of breathing was slower in the evening than in the morning, and in three additional instances significant alterations were not noted. In the remaining nine observations the breathing was faster in the evening by two or more breaths per minute, and in five of these the difference was marked. The average respiratory rate was 20 in the morning and 23 in the evening—an increase of 15 per cent. (The individual figures in the tables are averages of the respiratory rate for six or more minutes. Hence, differences of two or more can be regarded as significant.)

The ventilation was greater in the morning in two of twelve observations, the evening ventilation being greater in the other ten instances. (When one recalls the influence of psychic disturbances on ventilation and the difficulties inherent in making respiratory measurements on dyspneic patients it is not surprising that occasional exceptional results occur.) The average ventilation in the evening (9.66 liters) was approximately 15 per cent greater than that in the morning (8.36 liters).

Variations in the tidal air were inconstant. Some patients with rather severe evening dyspnea breathed more deeply in the morning, but in other observations the reverse change was noted, and the average values for tidal air were practically identical.

In chart 1 are shown spirometric tracings which represent marked differences in the rate of breathing at the different hours of the day. The variations usually observed were somewhat less striking than these but were usually qualitatively similar.

The consumption of oxygen was greater in the evening nine times and unchanged from the morning value twice, the average increase in the eleven observations being approximately 10 per cent.

Vital capacities were compared in twenty-three instances, and in twenty-two of these it was greater in the morning than in the evening. In six observations the difference was so small as to be within the limits of error of the methods used, but in the remaining sixteen com-

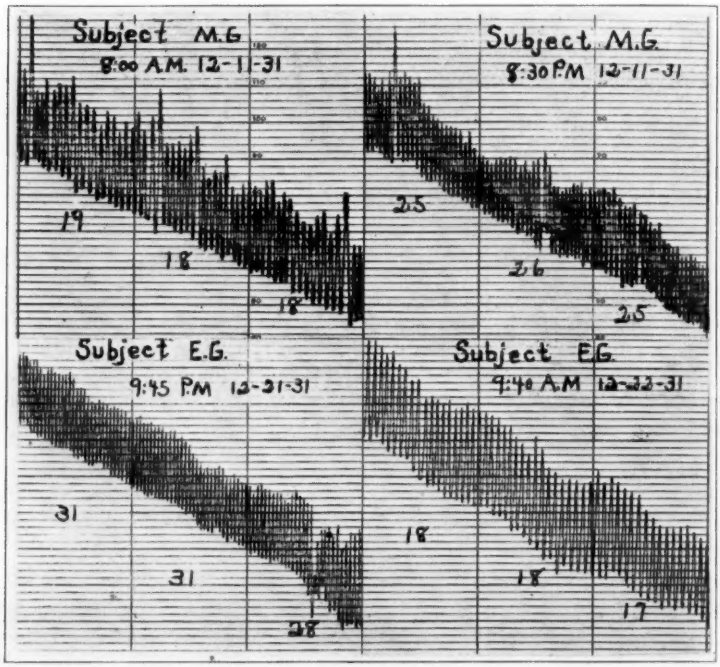

Chart 1.—The two upper curves represent observations made in the morning and afternoon, respectively, for the same patient. The two lower curves were obtained from another subject, the one on the left being taken in the afternoon and the one on the right the following morning. Both of these patients had more marked respiratory distress in the evening than in the morning and exhibited well marked increase in respiratory rate and in ventilation. In less dyspneic patients the differences were usually not as marked as these.

parisons the difference was 100 cc. or more. The average change in vital capacity in the evening was a decrease of 180 cc. or approximately 8 per cent as compared with the value in the morning. This slight but consistent decrease in the vital capacity in the evening did not occur on the days on which special therapeutic procedures were instituted.

Such measures often caused a reversal of the usual findings, the vital capacity being greater later than early in the day. The curves in chart 2 illustrate this fact. Following diuretics, phlebotomy or the administration of morphine the patients experienced a lessening of the dyspnea and coincidentally there was some rise in the vital capacity. As our study deals only with the mechanism of the dyspnea which is worse in the evening, all observations made on days when such therapeutic measures were instituted have been discarded from consideration.

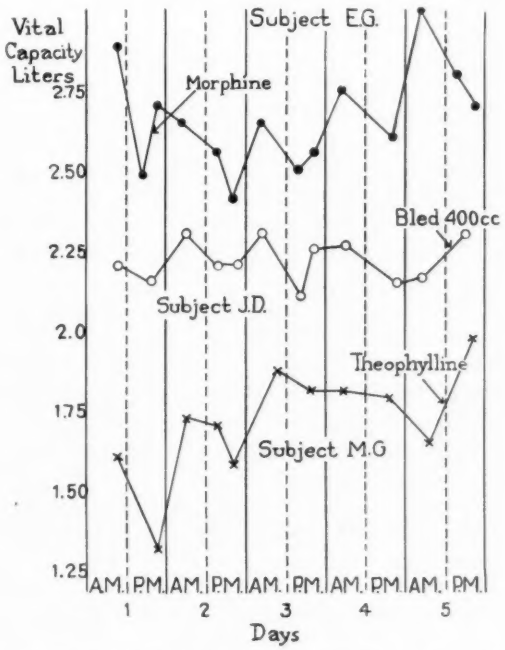

Chart 2.—These curves are illustrative of the usual slight reduction of vital capacity in the evening as compared to the morning in patients who were kept in bed but given no treatment. Any therapeutic measure administered during the day was likely to be attended by a reversal of the usual relationship.

As has been mentioned, control studies were made on subjects without cardiac disease and on persons with cardiac lesions but without evening dyspnea. For the sake of brevity the complete data for these two groups of subjects are omitted, but in table 3 the average values obtained for these groups are compared with those of the dyspneic patients.

As regards the circulatory functions, it can be seen that neither group of patients with cardiac disease exhibited variations in cardiac

rate, whereas the subjects without cardiac disease had slightly faster rates in the evening than in the morning. Significant diurnal changes in systolic blood pressures were not observed in any of the groups, although the average systolic pressure was highest in the dyspneic patients and lowest in persons in the group without cardiac disease. The diastolic blood pressure was about 10 per cent lower in the evening than in the morning in both of the control groups. It seems probable that this finding is to be interpreted as evidence of some vascular relaxation during the course of the day. The dyspneic patients failed to show this decrease in diastolic blood pressure in the evening. However, it seems extremely unlikely that this fact can account for the dyspnea, as the average diastolic pressure when they were dyspneic was exactly the same as the average value observed in the morning when they were free from dyspnea. Although we have no evidence concerning the exact cause of the absence of the decline in diastolic pressure in the evening, it seems likely that there may be some relation between this factor and the as yet unexplained tendency for the blood pressure to be elevated in persons with congestive heart failure (*Stauungshochdruck*).

The consumption of oxygen behaved similarly in all groups, the average value being approximately 10 per cent higher in the evening than in the morning. The average consumption of oxygen of the patients with congestive cardiac failure was only about 5 per cent higher than that of the other groups. This fact is noteworthy in view of the rather numerous reports in the literature of elevated metabolic rate in persons with cardiac disease.

Despite the greater consumption of oxygen, the respiratory rate and ventilation of the subjects with normal hearts were not significantly increased in the evening. The persons with cardiac disorders but without evening dyspnea had no increase in respiratory rate, but did have, on the average, a slight increase in ventilation in the evening. However, patients with evening dyspnea had a definite increase in both of these functions during the day, the average evening values being about 15 per cent above the morning level.

In all three groups the average values for the vital capacity were lower in the evening than in the morning, but in the nondyspneic subjects the difference was extremely small and less than the error of measurement. In the dyspneic patients the average difference was considerably greater, occurred in almost every instance (table 2) and was beyond the error of measurement.

When the various groups are compared with each other as regards respiratory measurements it is seen that the respiratory rates and ventilation were least in the subjects without cardiac disease and greatest in the dyspneic patients. As would be expected, the reverse relationship

was found in regard to the vital capacity. In each of these functions the patients with cardiac disease but without dyspnea showed an intermediate value.

For the purpose of expressing the degree of dyspnea in a more nearly quantitative form calculations were made of the quotient: $\frac{\text{ventilation per minute}}{\text{vital capacity}}$. It was shown in a previous study that this ratio is a fairly accurate numerical guide to the intensity of dyspnea produced by exertion; and the same relationship holds good for dyspnea at rest, provided there is no obstruction to the breathing. The values for this

TABLE 3.—*Average Values for Morning and Evening Circulatory and Respiratory Measurements*

	Subjects Without Cardiac Disease			Subjects with Cardiac Disease but No Dyspnea			Subjects with Cardiac Disease and Evening Dyspnea		
	Morning	Evening	Change from Morning Value, per Cent	Morning	Evening	Change from Morning Value, per Cent	Morning	Evening	Change from Morning Value, per Cent
Cardiac rate per minute....	81	87	+ 7.4	73	73	0	86	86	0
Systolic blood pressure, mm. of mercury.....	126	123	— 2.4	140	137	—2.1	159	161	+ 1.3
Diastolic blood pressure, mm. of mercury.....	81	72	—11.1	75	68	—9.3	76	76	0
Respiratory rate per min.	13	14	+ 7.7	17	17	0	20	23	+15
Ventilation per minute, liters.....	6.65	6.70	+ 0.8	7.56	8.25	+9.1	8.36	9.66	+15.6
Oxygen consumption per minute, cc.....	248	276	+11.3	251	269	+7.6	261	286	+ 9.6
Vital capacity, liters.....	3.96	3.88	— 2.0	2.92	2.89	—1.0	2.51	2.32	— 7.6
Ratio of ventilation to vital capacity.....	1.68	1.73	+ 3.0	2.60	2.85	+9.6	3.33	4.16	+24.9

quotient were highest in the dyspneic patients and lowest in the subjects without cardiac disease, as shown in table 3. In the latter subjects there was little difference between the figures for morning and for evening, but the patients with dyspnea exhibited a marked rise in this quotient, which was about 25 per cent higher in the evening than in the morning. This does not mean, however, that their dyspnea was greater only by one fourth in the evening than in the morning. There is a threshold value above which this quotient must rise before a patient feels dyspneic at all. Once this quotient (which we have called the "resting ventilation index" in order to distinguish it from the value obtained with exercise, which has been called the "ventilation index") passes above the threshold of dyspnea any further rise is associated with a relatively great increase in the degree of dyspnea.

An analogy will serve to make the last sentence somewhat clearer. Let us suppose that a person has a renal threshold for sugar of exactly 180 mg. per hundred cubic centimeters of blood. Now if the blood sugar rises from 100 to 170 mg. he will have no glycosuria. At 180 mg. there will be just the slightest trace of sugar in the urine. But from that point on even a very slight further increase in blood sugar will result in a relatively marked increase in the degree of glycosuria. A rise of 10 per cent in the blood sugar (to 200 mg.) will be attended by an increase of much more than 10 per cent in the amount of sugar in the urine.

By numerous observations on many patients in the course of the past two years we have established the fact that (under the conditions in which our observations have been carried out, i. e., using valves of a given resistance) the threshold for dyspnea at rest lies in the general region of values of from 3 to 4 for the resting ventilation index. The threshold is higher in phlegmatic persons and lower in excitable ones (as is the threshold to pain), but in all those who are not either obviously hypersensitive or in a state of depressed sensibility because of drugs or disease the threshold is in the region mentioned.

Now, as can be seen from table 3, the persons in the first two groups have values for the resting ventilation index which are below this threshold region. The patients with congestive failure had, however, resting ventilation indexes which were on an average just at this level in the morning, and which exceeded it in the evening as dyspnea set in.

The data which have been presented seem to indicate that the explanation for evening dyspnea is not to be found in changes in the composition of the blood but is related to diurnal changes in the vital capacity and in the ventilation, the alterations in both of these functions being in the direction of increased dyspnea. We do not intend to imply that a person is more short of breath because he has a greater ventilation, but mean that both the subjective sensation of respiratory distress and the increase in ventilation are parallel responses to the same stimulus. The increase in ventilation, being objective, can—when considered in relation to the vital capacity—be used as a measure of the distress. Thus the problem of the cause of evening dyspnea involves at least two questions: 1. Why is the ventilation greater in the evening? 2. Why is the vital capacity lower in the evening?

At first thought one might suppose that the increase in metabolic rate in the evening was the direct and immediate cause of the greater ventilation. However, the data do not support such a conclusion, because:

1. The ventilation of the patients with congestive heart failure increased in greater degree than did their metabolic rates.

2. The control subjects exhibited as great an increase in consumption of oxygen in the evening as did the dyspneic patients, but the former subjects had either no change or a much smaller increase in ventilation.

Another possibility suggested itself as to the cause of the increase in ventilation. It was shown in a previous study [7] that certain procedures leading to a decrease in the vital capacity of dogs caused reflex acceleration of breathing and augmentation of ventilation, the afferent path from the lungs being through the vagus nerves. Hence, one might conclude that the greater ventilation associated with evening dyspnea was due to reflex respiratory stimulation associated with events causing the decline in vital capacity which took place during the day. However, such a conclusion did not seem to us justifiable without further experimental confirmation because the daily decline in vital capacity in our patients was often very slight and sometimes less or barely more than the experimental error, whereas, in the study previously referred to only the effects of relatively great diminutions in vital capacity were investigated. Therefore the question arises: Can an increase in pulmonary congestion of such slight degree as to produce a barely measurable decline in vital capacity cause reflex stimulation of breathing? In order to answer this question it was necessary to resort to animal experimentation.

EXPERIMENTS ON DOGS

The animals were anesthetized with barbital and prepared according to the technic described in a previous study.[7] The chest was opened, a cannula was inserted in the left primary branch of the pulmonary artery, and the left pulmonary veins were tied. The wound was then sutured in such a way as to make an air-tight closure around a small piece of rubber tubing which was connected to the cannula. By this method it was possible to produce at will "congestion" of the left lung, since blood introduced into the artery could not escape from the lung.

Following the operative procedure artificial respiration was discontinued, and the animal was allowed a few minutes in which to establish spontaneous breathing at a constant level. Observations were then made concerning the effect of introducing small amounts of blood into the left lung. In order to determine whether the effects of congestion on the respiration were of the same order of magnitude as those produced by other procedures causing a similar decrease in the volume of the lung, observations were also made on the effect of introducing similar amounts of air into the pleural cavity. It has been previously shown that either of these procedures leads to a well marked reflex stimulation of respiration.

Typical results are shown in charts 3 and 4. The introduction of 25 cc. of air into the pleural cavity was usually attended by an immediate but slight and temporary increase in the respiratory rate. Different animals reacted differently, but in none of them was there a sustained increase in the rate of breathing of more than 2 respirations per minute. When 25 cc. of blood was introduced into the pul-

7. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: Studies in Congestive Heart Failure: XV. Reflex Versus Chemical Factors in the Production of Rapid Breathing, J. Clin. Investigation **11**:133, 1932.

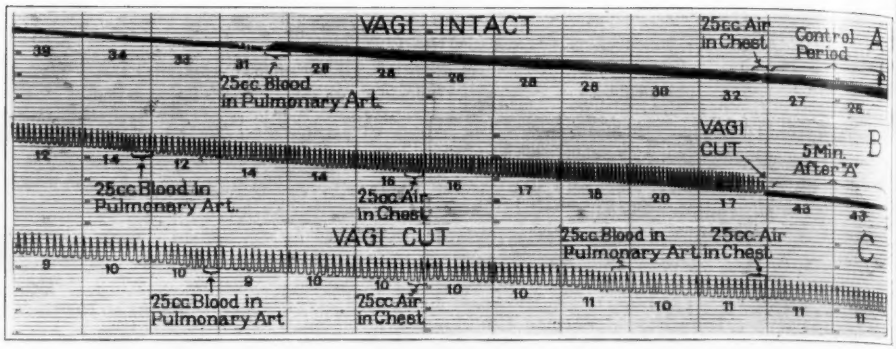

Chart 3.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers beneath the curves indicate the respiratory rate per minute. Curve *A* represents conditions with the vagus nerves intact. Injection of 25 cc. of air into the right pleural cavity caused a temporary stimulation of respiration, whereas progressive and sustained effects followed injection of a similar amount of blood into the vascular bed of the left lung, from which it could not escape because the veins were ligated (see text). Cutting the vagus nerves slowed the respiratory rate (*B*) and the same procedures which had previously caused stimulation of respiration were without effect.

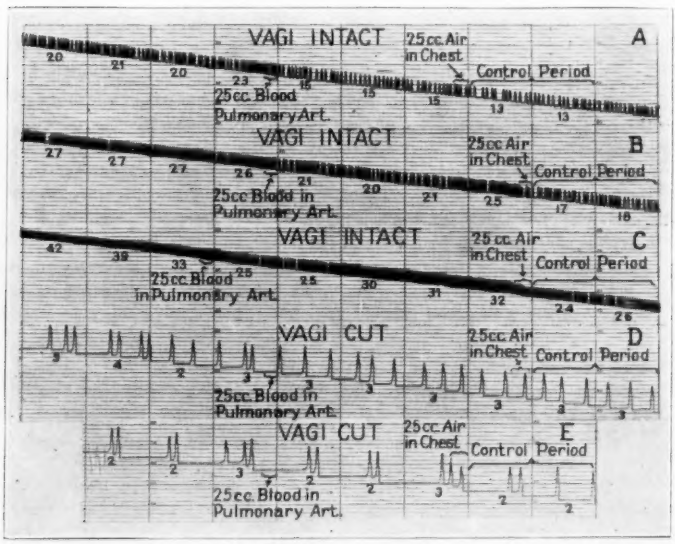

Chart 4.—The curves pass from right to left. The distance between two adjacent vertical lines represents one minute. The numbers beneath the curves indicate the respiratory rate. Injection of blood into the vascular bed of the left lung caused in each instance a more sustained stimulation of respiration than did injection of air into the right pleural cavity (*A, B, C*). After vagotomy the same procedures were without significant effect (*D, E*).

monary vascular bed, the increase in respiratory rate and in ventilation was usually more pronounced, the effect was always longer sustained, and in several experiments the increase in breathing was progressive over a period of several minutes. In vagotomized animals significant effects on respiration were never produced by either of the procedures in question.

These experiments show clearly that pulmonary congestion causes reflex stimulation of respiratory rate and increase in ventilation, provided the increase in respiratory rate is not too extreme—in which cases the very shallow breathing may be associated with diminished minute ventilation. They also indicate that congestion is relatively more effective than pneumothorax in stimulating breathing.

It is not likely that an anesthetized dog is more sensitive to reflex respiratory stimulation than a conscious man. Therefore, since the degree of congestion produced by 25 cc. of blood in a dog's lung is sufficient to cause marked increase in breathing, it seems justifiable to conclude that the degree of congestion which can produce a decrease of from 100 to 300 cc. in the vital capacity of man (in the evening as compared to the morning) could have been responsible for the increase in respiratory rate and ventilation which our patients exhibited in the evening.

COMMENT

There is ample clinical and experimental evidence to indicate that the chief cause of the decreased vital capacity in persons with cardiac failure is congestion of the lungs. The diminution and increase of vital capacity as congestive failure develops and disappears, when taken in conjunction with the fact that the lungs of patients dying of cardiac failure almost invariably show evidence of chronic engorgement, constitute convincing although indirect evidence that congestion is the chief cause of the decrease in vital capacity in such patients. Direct experimental confirmation of this conclusion is afforded by the experiments of Drinker, Peabody and Blumgart,[8] who found that compression of the pulmonary veins of the cat resulted in decrease in the pulmonary air space in these animals.

The data which have been presented seem to indicate that evening dyspnea is to be attributed to an increase in the degree of preexisting pulmonary congestion, which has two effects: In the first place it lowers the vital capacity and thereby tends to cause greater respiratory distress for any given level of ventilation. In the second place the greater pulmonary congestion, even if so slight as to cause a barely measurable decline in vital capacity, causes reflex stimulation of respiration with a resulting increase in the rate of breathing and in the minute ventilation. The sum total of these effects is to produce a rise in the quotient, $\frac{\text{ventilation}}{\text{vital capacity}}$, which is a measure of the degree of dyspnea. The average increase in this quotient in the evening as compared to the morning

8. Drinker, C. K.; Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, J. Exper. Med. **35**:77, 1922.

was 25 per cent. Such a change would be negligible in a person with normal lungs, but in a patient whose respiratory reserve is already lowered in the morning this change may be sufficient to produce considerable subjective respiratory discomfort in the evening.

Why are patients' lungs usually more congested (as revealed by the decrease in vital capacity) in the evening than in the morning? The answer to this question seems fairly obvious. In the morning the body functions are at a low ebb. Even though the patient remains in bed, there is a slight increase—which was, on the average, about 10 per cent in our cases—in metabolic rate during the day. It is well known that an increase in the activity of organs tends to be associated with an increase in their supply of blood. Hence, the venous return to the heart must be somewhat greater during the latter part of the day than in the morning, and the output of the right ventricle will tend to increase. If the left ventricle has less reserve power than the right ventricle (i. e., if the degree of dilatation of the left ventricle is relatively greater than that of the right) it will be less able to expel the incoming blood, and congestion of the lungs will necessarily result. In order for this to occur there need be no measurable decrease in the output of the left ventricle. A difference of 10 cc. per hour would account for the decrease in vital capacity which our patients showed. If the heart rate is 80 per minute the right ventricle only needs to pump about one thirtieth of a drop more blood at each beat than the left in order for enough additional congestion to occur in a period of twelve hours to account for the phenomena observed.

It should be pointed out that the sequence of events mentioned is not in accord with the "diminished cardiac output" theory of dyspnea. It is the increase in output of the right ventricle (owing to the greater activity of the body in the waking as compared to the sleeping state) which initiates the events leading to dyspnea. Although one has to postulate a relative diminution in the output of the left ventricle as compared to the right, the change is so slight—i. e., a difference of perhaps 100 or 200 cc. out of a total cardiac output of at least 2,000 liters in twelve hours—as to be entirely without significance when viewed as a decrease in the blood supply to the tissues. It has been customary to think of cardiac dyspnea of all types as being of chemical origin and as due to an insufficient supply of blood to the respiratory center. Our observations on evening dyspnea indicate that, like orthopnea and the dyspnea of mild exertion, it is of reflex origin, is due to "back pressure," and that it need not be associated with any measurable change in the minute cardiac output.

SUMMARY

A comparison has been made between morning and evening values of the gases in arterial blood and of respiratory and circulatory functions in a group of patients who had congestive heart failure and who suffered from dyspnea which was more marked in the evening than in the morning. The following results were obtained: 1. The oxygen capacity of the blood tended to be higher in the morning, and the oxygen saturation was usually greater in the evening. The differences were usually so slight as to be negligible.

2. Consistent variations were not observed in the hydrogen ion concentration, the carbon dioxide content or the carbon dioxide pressure of the blood. On an average the blood was slightly more alkaline in the evening and had slightly lower values for carbon dioxide content and carbon dioxide pressure.

3. No consistent alterations in heart rate or blood pressure were observed.

4. The consumption of oxygen was about 10 per cent higher in the evening than in the morning. The respiratory rate and minute ventilation were greater in the evening by an average of 15 per cent. The vital capacity was slightly lower in the evening in practically every instance, but the difference found was often not greater than the error of measurement.

5. Control observations were made on a group of patients without cardiac disease and on a group of patients with cardiac disease but without dyspnea. These two groups differed from the dyspneic subjects in the following results: (*a*) Their diastolic blood pressures were usually lower in the evening than in the morning, whereas no change was observed in the patients with dyspnea.

(*b*) Although their increase in consumption of oxygen in the evening was of about the same degree, they exhibited no increase in respiratory rate and much smaller increases in ventilation. Likewise, the control group did not exhibit constant changes in vital capacity.

Experiments were performed on dogs in order to determine whether pulmonary congestion of such slight magnitude as to cause a barely measurable decrease in vital capacity could cause reflex stimulation of respiration. The following results were obtained: 1. In animals with intact vagus nerves the introduction of as little as 25 cc. of blood into the left pulmonary artery (the left pulmonary veins being tied) led to a well marked increase in respiratory rate and in ventilation.

2. Introduction of the same amount of air into the right pleural cavities of the same animals caused less marked and less sustained respiratory stimulation.

3. After bilateral vagotomy the introduction of blood or air produced no significant changes in respiration.

As a result of these clinical and experimental observations the following conclusions are drawn:

1. The pulmonary afferent fibers of the vagus nerve are extremely sensitive to pulmonary congestion. A very small amount of excess blood in the pulmonary vascular bed causes a well marked reflex stimulation of breathing.

2. Evening dyspnea in patients with congestive heart failure is probably to be attributed to reflex respiratory stimulation and a decrease in vital capacity because of an increase in the degree of the preexisting pulmonary congestion. The greater congestion of the lungs in the evening than in the morning is believed to be due to greater bodily activity during the waking hours.

NATURE AND SIGNIFICANCE OF HEART SOUNDS AND OF APEX IMPULSES IN BUNDLE BRANCH BLOCK

J. K. LEWIS, M.D.
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King [1] and King and McEachern [2] described a group of physical signs by means of which they were able to recognize bundle branch block in 85 per cent of patients with this condition. These signs consist of a visible or palpable double apical impulse, reduplication of the first sound at the apex, an asynchronous first sound and murmur and asynchronous systolic murmurs. The abnormal impulse was found in over 80 per cent of their patients and was regarded as the most important sign. A reduplicated first sound was present in 56 per cent of their patients, and the other signs mentioned occurred less frequently. In a number of patients they obtained graphic evidence of the presence of a double systolic apical impulse by photographing the movements of a straw or its shadow attached to the chest wall at the site where the abnormal impulse was seen or felt.

No other systematic study of the physical signs in bundle branch block has been made, but it is evident from reports dealing with other aspects of this condition [3] that abnormal physical signs of various kinds have been observed. Canter or gallop rhythm and reduplicated first sounds have been described, and occasionally reference has been made to the occurrence of an abnormal impulse. The type of electrocardiograms which White [4] found associated with gallop rhythm also points to the fact that abnormal physical signs are common in bundle branch block. Intraventricular block was present in 38 per cent of the sixty-four electrocardiograms which he obtained in a group of one hundred patients with gallop rhythm, and was the most frequent electrocardiographic characteristic observed. As intraventricular block is not a

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1. King, J. T.: The Clinical Recognition and Physical Signs of Bundle-Branch Block, Am. Heart J. **3**:505, 1928.

2. King, J. T., and McEachern, D.: The Nature of the Physical Signs of Bundle-Branch Block, Am. J. M. Sc. **183**:445, 1932.

3. (*a*) Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, Arch. Int. Med. **13**:803 (May) 1914. (*b*) Cowan, J. R., and Bramwell, J. C.: The Clinical Aspects of Bundle Branch Block, Quart. J. Med. **19**:95, 1925. (*c*) Bach, F.: On the Clinical Significance of Right Bundle-Branch Block, ibid. **23**:261, 1930.

4. White, P. D.: The Clinical Significance of Gallop Rhythm, Arch. Int. Med. **41**:1 (Jan.) 1928.

frequent abnormality, his findings indicated that gallop rhythm is a common physical sign in this condition. Protodiastolic gallop rhythm was the most frequent type; systolic gallop rhythm was present in one patient. While the foregoing observations indicate that abnormal physical signs of one kind or another are not uncommon in patients with bundle branch block, none of them suggests that these signs are useful in the diagnosis of this condition.

Since King's [1] first paper appeared, Hill,[5] Christian [6] and Graybiel and Sprague [7] have commented on the possibility of making the diagnosis of bundle branch block by the use of these signs. Hill and Graybiel and Sprague did not feel that the diagnosis could be made on clinical grounds, but Christian stated that one could make the diagnosis at the bedside with the aid of these signs.

A few observations on the character of the physical signs in bundle branch block have been made by means of records of the heart sounds and apex cardiograms. T. Lewis [8] recorded abnormal sounds which he called reduplicated first sounds [9] in four patients. In these patients the abnormality was due to an extra sound occurring late in diastole. It followed the P wave by a longer interval than the extra sound in the average patient with gallop rhythm, and its appearance was often similar to that of the first heart sound. In another paper, T. Lewis [10] referred to this abnormality as canter rhythm. Battaerd [11] recorded the sounds

5. Hill, I. G. W.: Bundle-Branch Block: Clinical and Histological Study, Quart. J. Med. **24**:15, 1931.

6. Christian, H. A.: Diagnosis of Chronic Nonvalvular Heart Disease (Chronic Myocarditis), New England J. Med. **208**:574, 1933.

7. Graybiel, A., and Sprague, H. B.: Bundle-Branch Block; an Analysis of 395 Cases, Am. J. M. Sc. **185**:395, 1933.

8. Lewis, T.: Illustrations of Heart-Sound Records, Quart. J. Med. **6**:441, 1912-1913.

9. The meaning of this term is not always clear. Because the normal first sound does not begin until the beginning of systole, it is preferable to reserve the term "reduplicated first sound" or "double first sound" for those sounds which are entirely systolic in time, and to use the term "gallop rhythm" or "gallop sound" to describe the abnormal sounds which originate in diastole. This terminology will be used in this report. It is clear that King and McEachern [4] regarded the signs which they found as being systolic. The terminology of gallop rhythm has been discussed by Holt (Gallop Rhythm, Am. Heart J. **2**:453, 1927) and by Wolferth and Margolies (Gallop Rhythm and the Physiological Third Sound: I. Characteristics of the Sounds, Classification, Comparative Incidence of the Various Types and Differential Diagnosis, Am. Heart J. **8**:441, 1933).

10. Lewis, T.: Lectures on the Heart, New York, Paul B. Hoeber, Inc., 1915, p. 53.

11. Battaerd, P. J. T. A.: Further Graphic Researches on the Acoustic Phenomena of the Heart in Normal and Pathological Conditions, Heart **6**:121, 1915.

in a number of patients with bundle branch block and stated that the sounds and their time relation to the electrocardiogram were normal. Wolferth and Margolies [12] reported the occurrence of a double first sound in the records obtained from one patient with bundle branch block. MacLeod, Wilson and Barker [13] recorded the sounds in four patients with bundle branch block. The sounds were normal in one patient, but in the other three presystolic gallop rhythm was present. They pointed out that because of the time of occurrence of the extra sound it could not be attributed to asynchronism of the ventricles. These three observations bring the total number of records of abnormal sounds in bundle branch block to eight; in seven instances there was presystolic gallop rhythm.

Eppinger and Stoerk [14] and Kauf [15] reported the occurrence of a double systolic impulse in bundle branch block. Their records are not entirely convincing, however, and will be commented on later.

These observations indicate that abnormal physical signs are common in bundle branch block, but they leave some doubt as to their exact nature and diagnostic value. The present study was undertaken in an effort to obtain more information on these points by means of records of the heart sounds and apex cardiograms.

Twenty-three patients have been studied, twenty of whom had electrocardiograms fulfilling the criteria of Carter [3a] for the diagnosis of bundle branch block. The electrocardiograms of the three remaining patients did not fulfil all these criteria, but in each case the Q R S complex measured 0.1 second or more. They are included in this study because King and McEachern [2] found that patients with this type of electrocardiogram often have physical signs similar to those present in patients with bundle branch block. With two or three exceptions all of the patients in the Stanford University Hospitals or in the outpatient service in the past four years who were found to have bundle branch block have been studied. Records of the heart sounds have been obtained from all patients; records of the apex beat, from fourteen. In seven of the first patients examined no attempt was made to record the apex beat, and in three others in whom the apex beat could not be seen or felt, attempts to record it were unsuccessful.

12. Wolferth, C. C., and Margolies, A.: The Various Types of Extra Heart Sounds, M. Clin. North America **14**:897 (Jan.) 1931.

13. MacLeod, A. G.; Wilson, F. N., and Barker, P. S.: Observations on the Heart Sounds with Particular Reference to Gallop Rhythm and Sounds of Auricular Origin, Proc. Soc. Exper. Biol. & Med. **29**:1009, 1932.

14. Eppinger, H., and Stoerk, O.: Zur Klinik des Elektrokardiogramms, Ztschr. f. klin. Med. **71**:157, 1910.

15. Kauf, E.: Zur Diagnose des Schenkelblocks beim menschlichen Herzen, Ztschr. f. klin. Med. **98**:126, 1924.

METHODS

The records of the heart sounds were obtained by means of Frank's capsules by a method similar to that described by Wiggers and Dean.[16] The capsule membranes were made of collodion or a similar material[17] rather than of rubber. Electrocardiograms were made simultaneously with the records of the sounds. In each case the shadow of the galvanometer string and the beam of light from the sound capsule were photographed simultaneously on stationary paper to determine whether or not the two records were synchronous. This method has been satisfactory in recording abnormal sounds in a large number of patients. By recording the heart sounds and the electrocardiogram simultaneously, the exact time relations of the heart sounds to other events of the cardiac cycle can be determined.

Frank's capsules were also used to record the apex beat, but the capsule membrane was thicker and made of rubber, and the entire system from the receiver on the chest wall to the capsule was closed. Comparison of the time of the initial systolic deflection in the apex cardiogram with that of the Q R S complex does not reveal any marked delay. Apex cardiograms are not subject to exact interpretation, and their appearance in a given patient may be changed remarkably by slight changes in the position on the chest wall from which the records are obtained. However, in the majority of the records obtained from the patients in this group a relatively simple wave, for the most part positive (indicating an outward displacement of the chest wall beneath the receiver), was obtained from the position of maximum impulse. It seems reasonable to assume that such a record represents what one might feel as an impulse in that region.

RESULTS

The nature of the physical signs present in this series of patients, together with certain clinical data, is given in table 1. The patients are grouped according to the type of abnormal sign present.

In a few of the eight patients classified as having no abnormal physical signs small presystolic vibrations or small presystolic waves were recorded, but as these signs could not be detected on physical examination, these patients have not been classified with those having abnormal signs.

16. Wiggers, C. J., and Dean, A., Jr.: The Principles and Practice of Registering Heart Sounds by Direct Methods, Am. J. M. Sc. **153**:666, 1917.

17. The most satisfactory and durable membranes were made from Duco household cement thinned with amyl acetate. An exceedingly thin membrane can be made by dropping some of this material onto water.

The records obtained from three of the eight patients of this group are of interest because the sounds were recorded during bundle branch block and during cycles with a relatively normal Q R S complex. The

TABLE 1.—*Nature of the Records of the Heart Sounds and the Apex Cardiograms Obtained in Twenty-Three Patients with Bundle Branch Block*

Patient	Age	Sex	Rhythm	Blood Pressure	Heart Sounds	Apex Cardiogram
1*	48	M	Sinus	140/ 94	Normal	Normal
2	63	M	Sinus	184/120	Normal	Normal
3	58	M	Sinus	180/ 98	Normal	Normal
4	53	F	Sinus	170/110	Normal	Not recorded
5	58	M	Auricular fibrillation	230/120	Normal	Not recorded
6	60	M	Auriculoventricular block	144/ 90	Normal	Not recorded
7	80	F	Auriculoventricular block	220/ 88	Normal	Not recorded
8	64	M	Auricular fibrillation	124/ 74	Normal	Not recorded
9	50	M	Sinus	220/116	Presystolic gallop	Presystolic impulse
			Auricular fibrillation	200/110	Protodiastolic gallop	Protodiastolic impulse
10	44	M	Sinus	200/110	Presystolic gallop	Presystolic impulse
11	51	F	Sinus	160/ 92	Presystolic gallop	Presystolic impulse
12	60	F	Sinus	140/ 70	Presystolic gallop	Normal
13*	47	F	Sinus	142/ 84	Presystolic gallop	Normal
14	76	M	Sinus	170/100	Normal	Presystolic impulse
15*	51	M	Sinus	135/ 74	Presystolic gallop	Not recorded
16	60	F	Sinus	178/ 80	Presystolic gallop	Not recorded
17	60	F	Sinus	210/110	Presystolic gallop	Not recorded
18	50	F	Sinus	138/ 90	Double first sound	Normal
19	70	F	Auricular fibrillation	110/ 80	Double first sound	Normal
			Sinus	.....	Double first sound	Normal
20	64	F	Sinus	140/ 80	Double first sound	Normal
21	60	F	Sinus	200/130	Double first sound	Normal
22	59	F	Sinus	170/ 86	Double first sound	Not recorded
23	69	M	Auriculoventricular block	210/ 90	Normal	Double systolic impulse

* "Atypical" bundle branch block.

records obtained from one of these patients are shown in figure 1. At the time these records were made many ventricular complexes occurred with a Q R S complex of normal duration, although several electrocardiograms made at other times were typical of bundle branch

block. The record shows that the amplitude of the vibrations of the first sound is less during bundle branch block than during the other cycles. This change was not always as marked as in the portion of the records shown, but it was always present to some degree. In the other two patients with changes in the form of the Q R S complex—a patient presenting heart block and cycles with a Q R S complex of normal duration mixed with those of bundle branch block and a patient presenting intermittent periods of bundle branch block—changes in the appearance of the records of the heart sounds did not accompany the changes in the electrocardiograms. Apex cardiograms were not obtained from these patients or from two others of this group. While these records are of interest and illustrate the fact that changes in the form of the Q R S complex do not necessarily produce important

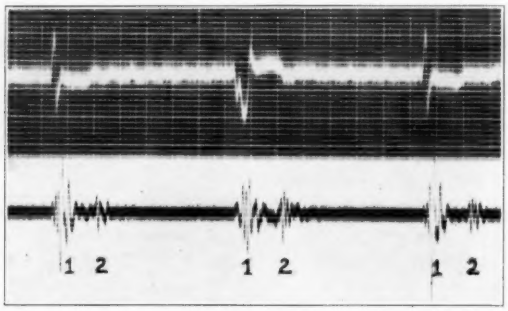

Fig. 1 (patient 5).—The second ventricular complex shown is that of bundle branch block and represents the usual type of Q R S complex present in this patient. The vibrations of the first sound accompanying this cycle are lower in amplitude than those of the other two cycles shown. These have a relatively normal Q R S complex.

changes in the character of the sounds, they have no particular bearing on the questions involved and need no further comment.

Examples of the records obtained from the nine patients with presystolic signs are shown in figures 2, 3, 4 and 5. The character of the sounds heard and the appearance of the records were similar, in the majority of patients, to the sounds heard and recorded in the usual patient with presystolic gallop rhythm. The only obvious difference between the records of gallop rhythm obtained from these patients and those obtained from patients without bundle branch block was the tendency for the sound responsible for the gallop to follow the P wave by a longer interval in the patients with bundle branch block, a point noted by T. Lewis [8] in the records that he obtained from patients with this condition. The time relations of these sounds and corresponding

impulses to the P wave and the Q R S complex are shown in table 2. The interval from P to the gallop sound, which ranged from 0.12 to 0.17 second, may be compared with an interval of from 0.08 to 0.14 second found by Wolferth and Margolies [18] in a group of patients with presystolic gallop rhythm. Although this interval was often within

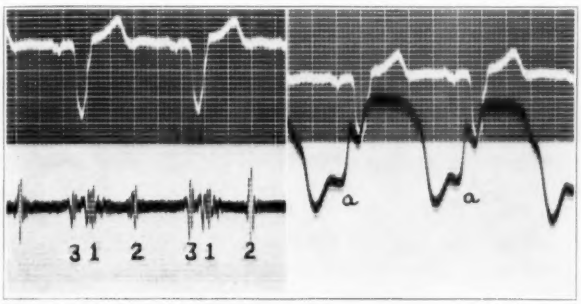

Fig. 2 (patient 9).—Presystolic gallop rhythm. The records of the heart sounds show a presystolic sound (*3*); the apex cardiograms, a presystolic impulse (*a*). (The gallop sounds and impulses will be indicated in the same manner in the records to follow.)

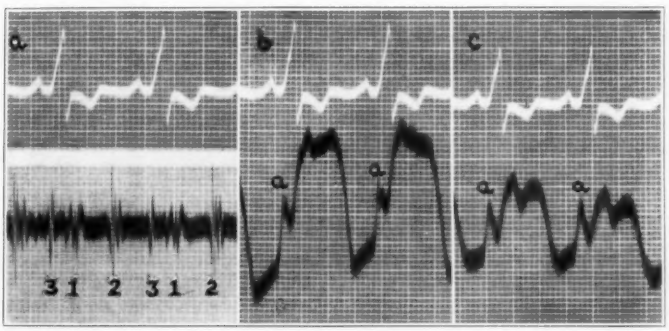

Fig. 3 (patient 10).—Presystolic gallop rhythm. Presystolic sounds and impulses are shown. The apex cardiograms in records *b* and *c* were obtained in adjacent areas. Those in record *c* show a double systolic wave in addition to the presystolic wave.

the range found by Wolferth and Margolies, in several patients it was considerably prolonged, so much so that the gallop sound preceded

18. Wolferth, C. C., and Margolies, A.: Gallop Rhythm and the Physiological Third Heart-Sound: I. Characteristics of the Sounds, Classification, Comparative Incidence of the Various Types and Differential Diagnosis, Am. Heart J. **8**:441, 1933.

the initial deflection of the Q R S complex by less than 0.02 second. This was the case in patients 10 and 12 (figs. 3 and 4) and patient 16. The prolongation of this interval brought the presystolic sound close to the first heart sound and was probably the factor responsible for the clinical interpretation of the sounds shown in figure 4 as a reduplicated first sound rather than as gallop rhythm. In this record the interval from P to the gallop sound is 0.15 second, and the interval from the beginning of the presystolic sound to the first heart sound is 0.07 second. During the course of this study the same prolongation of this interval was found in a number of patients with gallop rhythm but without bundle branch block and was apparently responsible for the same error in the clinical interpretation of the physical signs. It should be noted that other factors may modify the effect of the lengthening of

TABLE 2.—*Time Relations Between the Presystolic Sounds and the Electrocardiogram*

Patient	Interval in Seconds Between			
	P and R	P and Gallop Sound	R and First Heart Sound	Gallop Sound and First Heart Sound
9	0.20	0.17	0.09	0.12
10	0.16	0.15	0.09	0.10
11	0.18	0.13	0.06	0.11
12	0.16	0.15	0.06	0.07
13*	0.20	0.15	0.05	0.10
14	0.20	....	....	....
15*	0.20	0.12	?	?
16	0.16	0.14	0.07	0.09
17	0.18	0.12	0.06	0.12

* "Atypical" bundle branch block.

this interval on the proximity of the sounds. For example, in figure 3 (patient 10) and in figure 5 (patient 13) the interval from P to the presystolic sound is also 0.15 second, but the interval between the initial deflection of the two sounds is 0.1 second (compared with 0.07 second in figure 4), and the sounds were interpreted clinically as presystolic gallop rhythm. In figure 5 the modifying factor is a prolongation of the P R interval, and in figure 3 it is a prolongation of the interval between the initial deflection of the Q R S complex and the first heart sound. Prolongation of this interval was also present in other patients with bundle branch block and was noted by T. Lewis.[8] In this patient the interval was 0.09 second, considerably longer than that found in other persons by the same method.

Records of presystolic impulses are shown in figures 2 and 3 along with the corresponding records of the sounds. The impulses began earlier than the sounds, and in the patients in whom both sounds and impulses were present, the sounds occurred during the ascent or at the peak of the presystolic wave. The waves present in these records are

higher than those obtained in persons without palpable presystolic impulses, in respect both to their total height and to their height in proportion to that of the main systolic wave. This relation varied with

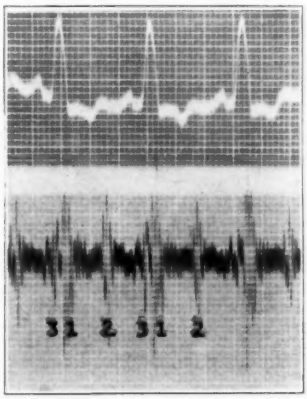

Fig. 4 (patient 12).—Presystolic gallop rhythm. The interval from the gallop sound to the first heart sound is short, measuring 0.07 second. The sounds heard were interpreted as a double first sound.

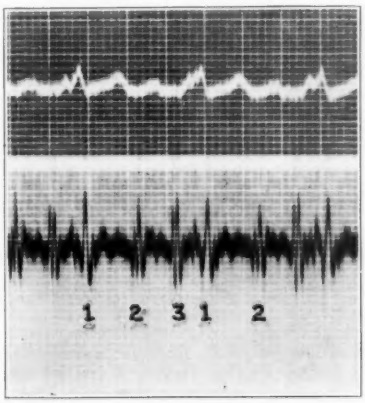

Fig. 5 (patient 13).—Presystolic gallop rhythm in a patient with "atypical" bundle branch block. Because of their low frequency, some of the vibrations of the first sound do not, in all probability, represent audible sound.

the position in which the record was obtained, a point illustrated by figures 3 *b* and *c*, but even in records showing the maximum systolic deflection obtainable in a given patient the height of the presystolic wave

may be almost one-half that of the main systolic wave. Such a record is shown in figure 3 *b*.

On palpation these impulses gave one the impression of an initial thrust, often abrupt, followed after a brief interval by a second more sustained rise. Some question may be raised as to the relation between the impulse felt and waves recorded in figure 3, since the records shown in figure 3 *c* show two systolic waves as well as a presystolic wave.

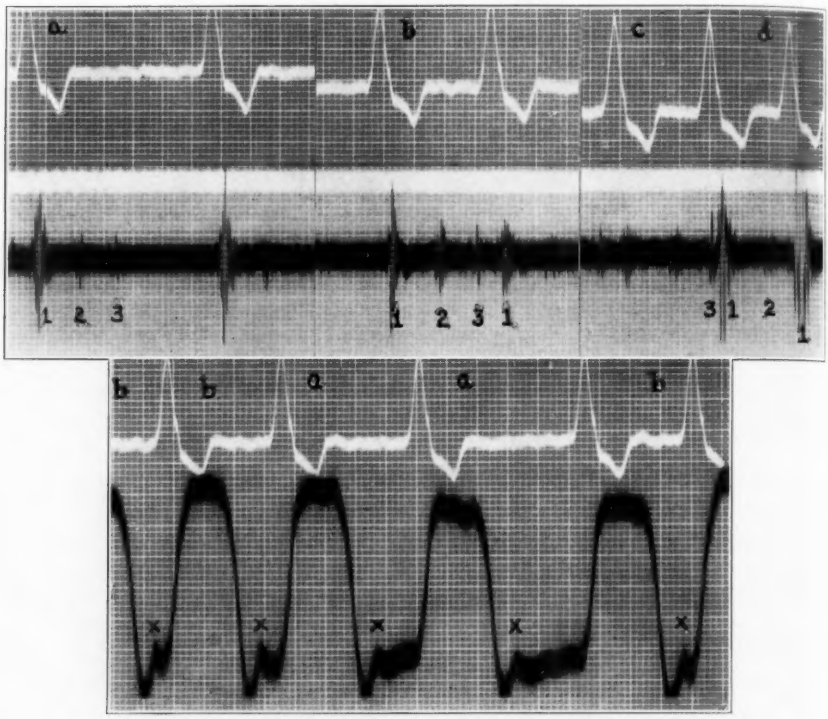

Fig. 6 (patient 9).—Protodiastolic gallop rhythm during auricular fibrillation. (Records obtained from this patient during sinus rhythm were shown in figure 2.) The protodiastolic sound (*3*) bears a definite relation to the preceding cycle. However, its relative position in the cardiac cycle depends on the length of diastole. In the long diastole of cycle *a* its position is that of a protodiastolic gallop sound, but in the shorter diastole of cycle *b* it occupies the position of a presystolic gallop sound. Cycles *c* and *d* are still shorter. In *c* the gallop sound (*3*) occurs after R but before the first sound of the following cycle; in *d*, in which the time of occurrence of the gallop sound and of the first heart sound of the following cycle are approximately the same, the first heart sound is exaggerated. The apex cardiograms show protodiastolic waves (*x*) which occur at approximately the same time as the protodiastolic sounds.

However, the fact that the presystolic wave is more prominent than the two systolic waves, together with the fact that the physical signs resembled those present in the other patients of the group, leads one to believe that the presystolic wave was the extra impulse felt. Records similar to this were not obtained in any other patient of this group.

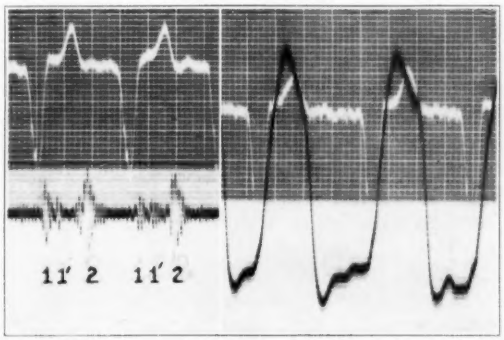

Fig. 7 (patient 19).—The records of the heart sounds show a double first sound (*1 1′*). The apex cardiograms are not remarkable. Records obtained from this patient during sinus rhythm also showed a double first sound.

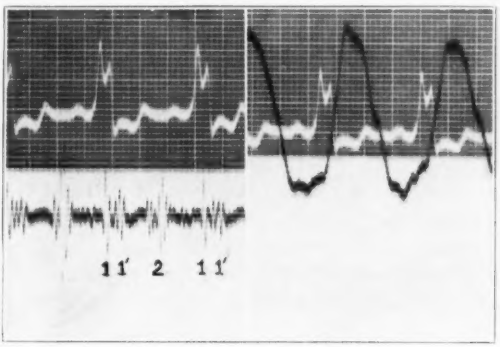

Fig. 8 (patient 20).—The records of the heart sounds show a double first sound (*1 1′*) and a double second sound (*2*). The apex cardiograms are not remarkable.

The changes which took place in the physical signs presented by patient 9 following the onset of auricular fibrillation are of sufficient importance to warrant a more detailed description. The records obtained from this patient before the change in rhythm are shown in figure 2. Similar records were obtained on five occasions covering a period of three years, the last being made two weeks before the onset of fibrillation and a month before the records shown in figure 6 were obtained.

In these records the presystolic sounds and impulses have disappeared and are replaced by protodiastolic sounds and waves. These are protodiastolic in the sense that they bear a definite time relation to the preceding cycle; actually they may fall in any part of a diastole. In a long diastolic pause, such as is present in cycle *a* of the sound and apex cardiogram tracings, the sound and impulse occur in early diastole, but during shorter cycles, such as *b*, they occur close to the first sound at about the time in the cardiac cycle that presystolic sounds and impulses occur. In cycle *c* of the sound record the protodiastolic sound actually begins after the R wave of the following cycle, and in cycles such as *d*, in which the time occurrence of the protodiastolic sound and wave is about the same as that of the first heart sound, the first heart sound is exaggerated just as it is in heart block when auricular and ventricular systole are close together. The interval from R to the protodiastolic

TABLE 3.—*Time Relations Between the Double First Sound and the Electrocardiogram*

Patient	Interval in Seconds Between	
	R and First Component of Sound	R and Second Component of Sound
18	0.07	0.15
19	0.08	0.19
20	0.08	0.17
21	....	....
22	0.04	0.11

sound varies from 0.65 to 0.7 second, with an average of 0.67 second, and the interval from R to the peak of the protodiastolic wave varies from 0.66 to 0.73 second, with an average of 0.69 second. The variation in this interval in different cycles depends, in part, on the length of the preceding cycle, the interval being shorter if the preceding cardiac cycle was shorter. This relation was noted by Wolferth and Margolies [18] in the records of sounds which they obtained from a patient with auricular fibrillation and gallop rhythm. Exaggeration of the first sound was present when it occurred from 0.62 to 0.67 second after the R wave of the preceding cycle. It seems likely that the variations in these intervals would be less if the measurements of both sounds and waves could be made from the same cycle, but it was not possible to obtain records of the sounds and apex cardiograms simultaneously.

The sounds heard in patient 9 were somewhat confusing. During long diastolic pauses the sounds could be identified as protodiastolic, but during shorter pauses one often got the impression of hearing a double first sound. The wave was not palpable.

The records obtained from two of the five patients with double first sounds are shown in figures 7 and 8. The sounds could be heard and recorded best along the left sternal border in the third or fourth intercostal space. In two patients the second heart sound was double. In the patient whose records are shown in figure 7 a change in rhythm from auricular fibrillation to sinus rhythm was not accompanied by a change in the character of the sound. In one of the patients included in this group a record of what appeared to be a double first sound was obtained, but an electrocardiogram was not made simultaneously with the records of the heart sounds. Two days later, when both records were taken simultaneously, the double first sound was absent, but as the total interval from the beginning of the first sound to the end of the second sound was the same on both occasions, it was concluded that the double sounds recorded in the first records were systolic.

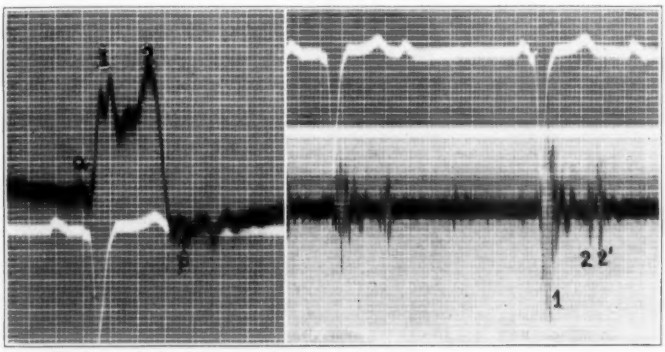

Fig. 9 (patient 23).—The apex cardiogram shows a double systolic impulse in which the first element is split. The auricular impulse (*a*) corresponding to the P wave immediately before the ventricular complex is separate from the systolic impulses. The next auricular wave cannot be identified, but the location of the corresponding P wave (determined by measuring the interval between the P waves on each side of the preceding ventricular complex) shows that it is also separate from the systolic impulses. The records of the heart sounds show an exaggerated first sound and a double second sound in the second cycle.

The time relations between the reduplicated sounds and the electrocardiogram are shown in table 3. In three patients the first element of the double sound occurred somewhat later in relation to the Q R S complex than the normal first heart sound. The two components of the double first sound began at an interval of from 0.7 to 0.11 second.

Double systolic impulses were not present in any of the four apex cardiograms obtained from the patients with reduplicated first sounds. The apex cardiograms obtained from two of them are shown along with the records of the sounds in figures 7 and 8.

The records shown in figure 9 are the only ones obtained showing a double systolic impulse. The electrocardiogram is that of complete heart block and bundle branch block of the rare form with a Q R S complex of 0.18 second. The first element of the double impulse, which is split, begins 0.04 second after the initial deflection of the Q R S complex, but the main rise of the second portion of the impulse does not begin until 0.12 second after the end of the Q R S complex. The auricular waves were palpable in this person, but in the cycle shown the auricular waves which precede and follow this particular ventricular beat are separate and therefore play no part in the production of the double impulse. The records of the sounds of this patient, also presented in figure 9, show an exaggeration of the first sound when P falls near the Q R S complex and a double second sound.

COMMENT

The records obtained from this group of patients show clearly that abnormal physical signs of two distinct types may be found in patients with bundle branch block. Although the group of patients studied is not large, both types of abnormal signs occurred with sufficient frequency to indicate that their presence is in some way related to bundle branch block or to the type of heart disease in which it occurs.

The presystolic signs cannot be due, as MacLeod, Wilson and Barker [13] pointed out, to asynchronism of the ventricles (or to bundle branch block itself), since they occur before the beginning of ventricular systole. The resemblance of the records of presystolic sounds and impulses obtained in these patients to those obtained in patients with gallop rhythm but without bundle branch block, their relation to auricular systole as shown by the relation of the sounds and impulses to the P wave of the electrocardiogram and the disappearance of the presystolic gallop sound and impulse shown in figure 6 following the onset of auricular fibrillation leave no doubt that these signs are of the same nature and are produced in the same manner as the presystolic gallop rhythm which occurs in patients without bundle branch block. The mechanism by which gallop sounds are produced has been adequately considered by T. Lewis,[10] Mond and Oppenheimer [19] and Wolferth and Margolies.[18] All that need be stated here is that according to their views the event which leads to the production of presystolic gallop sounds is auricular systole.[20] T. Lewis [10] and Wolferth and Margolies [18] have suggested that the corresponding event which leads to

19. Mond, H., and Oppenheimer, E. T.: Gallop Rhythm in Hypertension, Arch. Int. Med. **43**:166 (Feb.) 1929.

20. A logical explanation of the mechanism by which auricular systole leads to the production of sound will be found in the paper by Mond and Oppenheimer.[19]

the production of protodiastolic sounds is the rise in intraventricular pressure which occurs early in diastole. The close relation of the protodiastolic wave to the other events of the cardiac cycle and to the protodiastolic sound which is present in figure 6 during auricular fibrillation suggests that this wave represents this early diastolic rise in intraventricular pressure and supports the views of the authors just mentioned as to its relation to the production of protodiastolic sounds. Further evidence that the protodiastolic wave is related to sound production in the same way as auricular systole is provided by the exaggeration of the first heart sound when the wave (or the protodiastolic sound) and the first heart sound of the following cycle occur close together (figure 6, cycles *d*), an effect which is similar to the exaggeration of the first sound which occurs in heart block when auricular systole occurs close to the first sound.

As presystolic gallop rhythm cannot be produced by bundle branch block itself, some other reason must be sought not only for its presence but for the frequency with which it was found in this group of patients. Its occurrence in nine of twenty-three patients (seven of twenty if those with "atypical" bundle branch block are excluded) is a higher incidence than one would expect in an unselected group of patients with degenerative heart disease. The frequency with which it occurred may be compared with its presence in twelve of one hundred consecutive patients with cardiac disease examined by King and McEachern.[2] None of these twelve patients had bundle branch block. This observation is more remarkable if the degree of cardiac failure present is considered. Gallop rhythm is most frequently associated with advanced or acute stages of cardiac insufficiency, but in this particular group only one of the nine patients had definite congestive failure at the time of examination. All of the remaining patients had other evidence of heart disease, and several had experienced attacks of congestive failure, but all were ambulatory at the time of examination. The frequency with which White[4] found interventricular block in a group of patients with gallop rhythm also indicates that it is unusually common in this condition, but the significance of his findings in this connection may be questioned since he found protodiastolic gallop rhythm in the majority of his patients. Further comment in regard to the type of gallop rhythm will be made later.

The fact that gallop rhythm occurs in some patients with bundle branch block is reasonably explained by the similarity of the conditions with which these anomalies are associated. Gallop rhythm, in all probability, does not occur without definite impairment of cardiac function, and it is usually found in persons with degenerative heart disease, often with marked hypertension. Bundle branch block is also found, as a rule, in patients with degenerative heart disease, and while it may

occur in persons with good cardiac function it is almost always associated with other definite evidence of heart disease. No doubt marked hypertension favors the development of gallop rhythm, but it is by no means essential. A number of records of gallop rhythm have been obtained in this laboratory from persons with normal blood pressure, and it is a well known occurrence in patients with coronary occlusion and low blood pressure. It is not surprising, therefore, to find that a certain number of patients with bundle branch block and evidence of cardiac insufficiency have gallop rhythm. This explanation is adequate to account for the presence of gallop rhythm in a certain number of patients, but one cannot be certain that it accounts entirely for the unusual frequency with which it was found. It is possible that this finding is related to the severity of the heart disease associated with bundle branch block, a fact which is emphasized by the poor prognosis found in persons with bundle branch block by Willius,[21] Graybiel and Sprague [7] and others.

The fact that presystolic gallop rhythm was the type present in the records of all but one of the patients with gallop rhythm in this series and in all of the other records of gallop rhythm obtained in this condition should be noted, since the protodiastolic and the presystolic type appear to be of about the same significance and to occur with about the same frequency.[18] There is no obvious explanation for this observation. However, the fact that White [4] found protodiastolic gallop rhythm to be the most common form suggests that a larger series of records would show a more equal distribution of the type of gallop rhythm present. Although White's observations were based on clinical evidence alone and were therefore subject to error, since it is often difficult to distinguish between the two common forms of gallop rhythm without records of the sounds, it is likely that the majority of his observations were correct.

The late occurrence of the gallop sound in relation to the P wave noted by T. Lewis [8] and present in some of the records obtained from this group of patients also requires some comment. A complete explanation for this fact is not apparent, but the observations of Duchosal [22] on factors influencing this interval should be mentioned. He found that as the degree of heart failure became less, the interval from P to the gallop sound increased. The same relation appears to exist in this series of patients, since only one was suffering from a severe degree of congestive failure at the time of examination. However, the data obtained were not entirely comparable, since well marked changes in

21. Willius, F. A.: Arborization Block, Arch. Int. Med. **23**:431 (April) 1919.

22. Duchosal, P.: A Study of Gallop Rhythm by a Combination of Phonocardiographic and Electrocardiographic Methods, Am. Heart J. **7**:613, 1932.

the state of cardiac function did not occur during the period of observation, nor were there sharp differences in the degree of cardiac failure among persons of this group. The single patient with congestive failure had only a presystolic impulse.

A reduplicated first sound has been noted under various circumstances, and Wohlers and Duchosal [23] recorded it in a number of patients, but it does not appear to have been associated with any particular condition. Consequently, its demonstration in five patients with bundle branch block and the close time relations of the sounds and the Q R S complex in these patients suggest that the two are definitely related or, more specifically, that the reduplicated sound is due to asynchronism of the ventricles. However, sufficient data to show that asynchronism of the ventricles is present in bundle branch block or that it is accompanied by a reduplicated sound are not available. Eppinger and Rothberger [24] found a difference of 0.04 second in the time of onset of the pulse wave in the aorta and in the pulmonary artery after cutting one branch of the His bundle in the dog. On the other hand, Katz [25] found almost as great a degree of asynchronism (0.035 second) in the beginning of ventricular systole under ordinary experimental conditions. Wiggers [26] found still greater degrees of asynchronism in ventricular extrasystole, a condition which is not accompanied by reduplicated sounds. In three experiments made in this laboratory the sounds were recorded directly from the heart after the cutting of the right bundle branch. Although the number of experiments was too small to lead to any definite conclusion, the fact that a double first sound did not occur is worth mentioning.

The single record of a double systolic impulse does not provide sufficient evidence on which to base a discussion concerning the nature of this particular sign. The significance of the record might also be questioned because of the other unusual features present, namely, heart block and an unusually wide Q R S complex.

The recognition of the fact that abnormal signs were present was not difficult, but in some cases errors were made in the interpretation of the kind of abnormality. Occasionally presystolic gallop rhythm

23. Wohlers, H., and Duchosal, P.: Etude phonocardiographique des dédoublements du premier bruit du coeur, Arch. d. mal. du coeur **25**:1, 1932.

24. Eppinger, H., and Rothberger, J.: Ueber die Sukzession der Kontraction der beider Herzkammern, inbesondere nach einseitiger Blockierung der Erregungsüberleitung, Zentralbl. f. Physiol. **24**:1055, 1910.

25. Katz, L. N.: The Asynchronism of the Right and Left Ventricular Contractions and the Independent Variations in Their Duration, Am. J. Physiol. **72**: 655, 1925.

26. Wiggers, C. J.: The Muscular Reactions of the Mammalian Ventricle to Artificial Surface Stimuli, Am. J. Physiol. **73**:346, 1925.

was interpreted as protodiastolic gallop. The interpretation of presystolic gallop rhythm as a reduplicated first sound, which was made in patient 12 of this series and in a number of patients without bundle branch block, has already been commented on. It is probable that in these persons the judgment as to the time of occurrence of the abnormal sounds was influenced by the character of the sounds heard rather than by actual timing with other events of the cardiac cycle. The presystolic impulses were interpreted correctly, but it seems likely that this interpretation was influenced by the belief that a presystolic sound was present. In the patient in whom a double systolic impulse occurred, there was some doubt as to its exact nature because of the presence of palpable auricular impulses. However, the apex cardiograms showed that these played no part in the production of the double systolic impulse.

It is apparent from the nature and the difference in type of the abnormal physical signs found in the records obtained from this group of patients that such signs are not suitable for use as evidence of bundle branch block. Presystolic gallop rhythm, which made up over one half of the abnormal physical signs, cannot be related to bundle branch block. Its presence is determined largely by the state of cardiac function and the type of heart disease, not by the presence of bundle branch block. Although the gallop rhythm differs in some respects from that usually encountered, these differences are not necessarily related to bundle branch block, nor can they be easily recognized on physical examination. A reduplicated first sound might appear to be of some value as a physical sign because it is possible that it has a direct relation to bundle branch block and is not associated with any other condition. However, the frequency with which it occurs does not seem sufficient to warrant its use as an important diagnostic sign, and its usefulness is further reduced by the fact that it may occur under other circumstances or may be confused with presystolic gallop rhythm. The abnormal impulses in our patients were of little use as diagnostic signs. The presystolic impulses which accompanied presystolic sounds in a few cases have the same significance as the sounds, and the occurrence of a double systolic impulse but once in fourteen patients in this group does not warrant its consideration as a specific physical sign.

A comparison of the physical signs found by King and McEachern [2] with those found in this group of patients reveals marked differences. Reduplicated first sounds were noted in both series, but presystolic gallop rhythm, which was the predominant finding in our group of patients, was not noted by them, and a double systolic impulse, which was the most frequent sign found in their patients, could be demonstrated in but one of fourteen patients in our series. These differences are sufficiently marked to justify further comment.

The frequency with which presystolic gallop rhythm was demonstrated by records of the heart sounds in this group of patients, as well as its occurrence in seven of the eight records of abnormal sounds previously obtained in cases of bundle branch block (Lewis,[8] Wolferth and Margolies,[18] MacLeod and his co-workers [13]), provides definite evidence that this sign is rather common in persons with this condition. No doubt the frequency with which it occurs in a group of patients is influenced by other factors, particularly the degree of heart failure present, but it is unlikely that it is entirely absent in any large group of persons with bundle branch block. For this reason it seems possible that King and McEachern [2] interpreted presystolic gallop rhythm as a reduplicated first sound in some of their patients. The factors which may lead to such an error have already been commented on.

The occurrence of presystolic impulses in this series was not remarkable since impulses of this kind are well known in patients with gallop rhythm and are, in all probability, a part of the same phenomenon. In regard to the failure to find double systolic impulses more frequently, all that can be said is that by a method which was capable of demonstrating abnormal impulses in a number of persons a double systolic impulse could be recorded in only one of fourteen patients. In addition, it may be pointed out that some of the evidence brought forth to show the presence of a double systolic impulse is not entirely satisfactory. The records published by Eppinger and Stoerk [14] show three systolic waves, one rather high, and in several cycles a fourth wave, presystolic in time, which is about the same height as the small systolic waves. In view of the number of waves present and of the presence of a presystolic wave the use of this record as evidence of a double systolic impulse does not seem justifiable. The records published by Kauf [15] were made with a Jacquet sphygmograph, a device generally regarded as inadequate to record the form of such an impulse as the apex beat. The evidence which King and McEachern [2] obtained by taking motion pictures of the shadow of a straw attached to the apex beat is not conclusive since it does not afford a means of determining the time in the cardiac cycle at which the various impulses occur. This criticism does not apply to the evidence that they obtained by photographing the shadow of the straw simultaneously with the taking of the electrocardiogram. However, the interpretation of one of the records obtained in this manner is open to criticism. In this record (fig. 5 of their paper) the second component of an impulse interpreted as a double systolic impulse begins well after the T wave of the electrocardiogram but before the P wave and is therefore a diastolic event, unrelated to auricular systole. This record is also quite different from the other records of double systolic impulse which were shown in their paper. In these records (figs. 5 and

6 of their paper) the two impulses originate in systole. It is possible that the second impulse shown in figure 5 of their paper represents the impulse of protodiastolic gallop rhythm.

As additional evidence to support their conclusions concerning the nature of the physical signs, King and McEachern [2] cited the occurrence of double systolic impulses in heart block and auricular fibrillation as evidence that the impulses present in their patients were not related to auricular systole and were, therefore, a different phenomenon than presystolic gallop rhythm. It is obvious that this is true, and it is supported, in the case of heart block, by the demonstration of a double systolic impulse quite separate from the auricular impulses shown in the records in figure 6 of their paper, as well as in the records in figure 9 of this report. However, the record first commented on (fig. 5 of their paper) shows that an impulse can occur in diastole, unrelated to auricular systole, and be interpreted clinically as part of the double systolic impulse. It is possible that the protodiastolic wave present during auricular fibrillation shown in figure 6 of this paper represents a similar event. Although this wave was not demonstrable on physical examination in this instance, it is conceivable that it might become visible or palpable under other circumstances, such as, for example, a more severe degree of heart failure, and become subject to the same error in interpretation. The various positions which the protodiastolic sound occupied, particularly its position close to the first sound in cycles such as *c* in figure 6, indicate that it might easily be interpreted as a part of a reduplicated first sound.

While the foregoing comments concerning the difference in the character of the apex beat found in the two series of patients do not imply that the observations of King and McEachern are entirely erroneous, they cast considerable doubt on their conclusion that all of the abnormal impulses which they observed were systolic.

SUMMARY

The nature of the physical signs present in twenty patients with bundle branch block and in three patients with "atypical" bundle branch block has been determined by means of records of the heart sounds and apex cardiograms. Records of the heart sounds were obtained from all patients; apex cardiograms, from fourteen.

Physical signs of two distinct types occurred.

Presystolic gallop rhythm was present in nine patients. In three of these patients a presystolic impulse was associated with the presystolic sound; in one the impulse was the only sign present.

A reduplicated first sound, entirely systolic, occurred in five patients. A double systolic impulse was present in one patient. A reduplicated

first sound and a double systolic impulse were not found together in any of the patients studied.

The presystolic gallop rhythm present in these patients was the same as that found in persons without bundle branch block except for a tendency for the interval between the P wave and the gallop sound to be prolonged. The lengthening of this interval may be related to the absence of severe grades of circulatory failure in this particular group at the time of examination. The presence of gallop rhythm in bundle branch block could be accounted for by the fact that both conditions occur in the same general type of heart disease and under the same circumstances. It could not be related to the bundle branch block itself (or to asynchronism of the ventricles).

The incidence of gallop rhythm in the whole group was higher than that present in an unselected group of patients with degenerative heart disease. The explanation for this fact was not entirely clear, but the frequency of the anomaly appeared to be a reflection of the severity of the heart disease which accompanies bundle branch block.

The frequency with which a reduplicated first sound occurred and its close association with the Q R S complex suggest that it may be produced by asynchronism of the ventricles. However, evidence to prove or disprove this point did not appear to be adequate.

The nature of the physical signs present was not such as to permit their use as diagnostic signs of bundle branch block.

Dr. Garnett Cheney and Dr. William Dock provided several of the patients included in this study.

BLOOD CHOLESTEROL AND THYROID DISEASE

III. MYXEDEMA AND HYPERCHOLESTEREMIA

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Numerous observations on the blood cholesterol in thyroid disease have been made and reported in the literature. References to the more important of these were included in a previous communication from the Lahey Clinic.[1] Since then reports of further investigations have appeared; yet in most of these a relatively small number of cases have been studied and fewer still have been followed from time to time.

Levy [2] followed the variations in the blood cholesterol in exophthalmic goiter treated by roentgen rays, and found variable results. Of ten cases, however, six showed a cholesterol value of more than 230 mg. per hundred cubic centimeters. Such findings seem unusual, because in this study less than 1 per cent of the patients with exophthalmic goiter were found to have a cholesterol value of this magnitude. Hilman [3] concluded, as did Epstein,[4] that hypercholesteremia was definite evidence against exophthalmic goiter, but that there was no rule regarding the behavior in that disease. The latter conclusion was also drawn by Bonilla and Maya.[5] Epstein and Lande's [4] observations on the blood cholesterol in thyroid disease and other diseases have apparently received scant attention in this country, but they are referred to frequently in French publications on the subject.

The effect of administering desiccated thyroid on the blood cholesterol has been the subject of more recent observations. The drop in cholesterol and the rise in the basal metabolic rate in myxedema follow-

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From the Medical Department of the Lahey Clinic and the Chemical Laboratory of the New England Deaconess Hospital.

1. Mason, R. L.; Hunt, H. M., and Hurxthal, L. M.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism: Their Significance, New England J. Med. **203**:1273 (Dec. 25) 1930.

2. Levy, M.: The Variations in the Cholesterol in Basedow's Disease, Treated by Radiotherapy, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1844 (Dec. 14) 1931.

3. Hilman, M. L.: Cholesterolaemia in a Few Diseases of the Endocrine Glands, Vrach. delo **14**:13 (Jan.) 1931.

4. Epstein, A. A., and Lande, H.: Studies on Blood Lipoids: I. The Relation of Cholesterol and Protein Deficiency to Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922.

5. Bonilla, E., and Maya, A.: Der Wert Cholesterinämia in den Schilddrüsenkrankheiten, Endokrinologie **9**:171 (Sept.) 1931.

ing the use of thyroid was described first by Luden,[6] in 1918. Experimental work with animals confirmed earlier observations [1] that the cholesterol of the blood is decreased by the administration of either desiccated thyroid or thyroxine.[7] Eleven cases of myxedema were reported by me in collaboration with Hunt and Mason,[1] and the return of the blood cholesterol to normal with thyroid therapy was shown. Parhon and Ornstein [8] and Levy and Levy,[9] on the basis that the blood cholesterol is elevated in old age and arteriosclerosis,[10] treated patients for hypercholesteremia with thyroxine and claimed dramatic results. Apparently they entertained the belief that hypercholesteremia is a precursor of arteriosclerosis, but they apparently did not attribute this necessarily to thyroid deficiency. Higher cholesterol values were reported by Bloor, Buckner and Gibbs [11] for diabetic patients who show advanced arteriosclerosis, although this relationship was not found by Hunt.[12] High cholesterol values have been reported in arteriosclerosis without diabetes.[13]

A study of the blood cholesterol in mental disease has been made by several observers.[14] Apparently the incidence of hypercholesteremia

6. Luden, G.: Studies on Cholesterol: V. The Blood Cholesterol in Malignant Disease and Effect of Radium on the Blood Cholesterol, Collected Papers, Mayo Clinic, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 470.

7. (*a*) Westra, J. J., and Kunde, M. M.: Blood Cholesterol in Experimental Hypo- and Hyperthyroidism, Proc. Soc. Exper. Biol. & Med. **29**:677 (May) 1932. (*b*) Simonds, J. P., and Helpler, O. E.: Fat Tolerance in Experimental Hyperthyroidism, J. A. M. A. **98**:283 (Jan. 23) 1932.

8. Parhon, C. I., and Ornstein, I.: Influence of Thyroxin on Cholesterol and Lipaemia, Compt. rend. Soc. de biol. **108**:303 (Oct. 16) 1931.

9. Levy, M., and Levy, E.: Thyroxin Therapy of Hypercholesterolaemia, Presse méd. **40**:240 (Feb. 13) 1932.

10. Parhon, C. J., and Parhon, M.: Hypercholesterolaemia of the Aged, Compt. rend. Soc. de biol. **88**:231, 1923.

11. Bloor, W. R.; Buckner, E., and Gibbs, C. B: Cholesterol Ester in Diabetic Plasma, Proc. Soc. Exper. Biol. & Med. **30**:63 (Oct.) 1922.

12. Hunt, H. M.: Cholesterol in Blood of Diabetes Treated at New England Deaconess Hospital, New England J. Med. **201**:659 (Oct. 3) 1929.

13. Mjassnikow, A. L.: Cholesterol in Arteriosclerosis, Ztschr. f. klin. Med. **102**:65 (Aug.) 1925.

14. (*a*) Forsyth, W. L.: Hypocholesterolaemia in Dementia Praecox, J. Ment. Sc. **72**:219, 1926. (*b*) Schube, P. G.: Blood Cholesterol Studies in Mental Disease, Am. J. Psychiat. **12**:355 (Sept.) 1932. (*c*) Duncan, A. G.: The Serum Cholesterol in Mental Disorders, J. Ment. Sc. **76**:284 (April) 1930. (*d*) Shaw, B. H., and Sharpe, J. S.: The Significance of Cholesterol in Cellular Oxidation and Its Bearing on Mental Disorder, J. Ment. Sc. **77**:53 (Jan.) 1931. (*e*) Grabfield, G. P., and Campbell, A. G.: A Note on the Relation Between Blood Cholesterol and Basal Metabolic Rate, New England J. Med. **205**:1148 (Dec. 10) 1931. (*f*) Targowla, Badonnel, Berman: Cholesterolaemia in Mental Disease, Encéphale **18**:139, 1923. (*g*) Duncan, A. G.: Effect of Thyroid Administration on the Blood Cholesterol, J. Ment. Sc. **77**:332 (April) 1932.

is greater in mental than in general disease, although Looney [15] believed otherwise. The effect of the administration of thyroid on the cholesterol was studied by Duncan,[14g] and here again a marked drop was noted by him in all cases. Only two cases of twenty-two studied by him showed hypercholesteremia. Grabfield and Campbell [14e] stated that the blood cholesterol is a function of neither the basal metabolic rate nor thyroid activity.

High cholesterol values are reported in such rare conditions as xanthomatosis, Niemann-Pick's disease and Christian-Schüller's disease.[16] Desiccated thyroid, combined with anterior pituitary substance, was used in one case of Christian-Schüller's disease, with remarkable results.[16] In view of the usual ineffectiveness of the oral administration of anterior pituitary substance, it is likely that the result was brought about by desiccated thyroid.

Hypercholesteremia was observed by Tolstoi [17] in studies of the effect of a diet of meat and fat. Bloor, I believe, observed hypocholesteremia in two dogs fed a purely carbohydrate diet but he was unable to reproduce the findings.

Obstruction of the common bile duct by stone was found by Epstein [18] to give high values for blood cholesterol, and this has been confirmed in six cases by Wilkinson and me in the Lahey Clinic.

RESPONSE OF THE BLOOD CHOLESTEROL TO THE ADMINISTRATION OF THYROID IN NORMAL PERSONS

As stated earlier, the blood cholesterol is lowered on the administration of thyroid substance. In table 1 are shown the results obtained in giving thyroid to three subjects: one with a low normal, one with an appproximately average normal and one with a high normal cholesterol level.

POSTOPERATIVE FINDINGS

Typical postoperative myxedema is accompanied by hypercholesteremia. In almost every instance this means the finding of a cholesterol level of 230 mg. or more (or whatever the upper limit of normal is considered to be in a given laboratory). Occasionally, because of the wide range of cholesterol values for apparently normal persons, there may be found a person with undoubted myxedema and a blood choles-

15. Looney, Joseph: Personal communication to the author.

16. Rowland, R. S.: Lipoid Metabolism, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1920-1921, vol. 4, p. 214.

17. Tolstoi, Edward: The Effect of an Exclusive Meat Diet on the Chemical Constituents of the Blood, J. Biol. Chem. **83**:753 (Sept.) 1929.

18. Epstein, E. C.: Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, Arch. Int. Med. **50**:203 (Aug.) 1932.

terol level in the upper range of normal (from 200 to 230 mg. per hundred cubic centimeters). In myxedema, however, the per cent of increase in the blood cholesterol as a result of thyroid deficiency is, on the average, so much greater than the per cent of decrease in the basal metabolic rate that the cholesterol stands out in contrast to the metabolism as an indicator of thyroid deficiency. Hypometabolism is not an invariable finding in myxedema, and furthermore, it is frequently found in other conditions. Hypercholesteremia, on the other hand, is a relatively uncommon finding except in such obvious clinical conditions as diabetes, nephrosis, obstruction of the common duct and, perhaps, advanced arteriosclerosis.

TABLE 1.—*Effect of Administration of Thyroid on Blood Cholesterol in Three Apparently Normal Persons*

Time, Weeks	Basal Metabolic Rate, per Cent	Cholesterol, Mg. per 100 Cc.	Pulse Rate	Weight, Pounds	Thyroid
		Housewife, Aged 29			
5 days	—35, —37	133	84	146.5, 146	Started with 4 grains
4	—18	70	84	135	Reduced to 2 grains
2	+12	104	84	131	Reduced to 1 grain
		Physician, Male, Aged 36			
	—16	160	57	152.5	Started with 2 grains
8	—13	128	64	150.2	Started with 4 grains
4	— 8	108	74	151.2	Stopped at 4 grains
4	—17	154	58	149	
		Technician, Female, Aged 28			
	— 7	230	..	180	Started with 2 grains
2	+ 4	150	..	178	Stopped at 2 grains
2	—10	235	..	180	

POSTOPERATIVE HYPOMETABOLISM WITHOUT HYPERCHOLESTEREMIA

In chart 1 are shown findings in seventy-eight postoperative cases with metabolic rates of —10 per cent or lower and cholesterol values below 200 mg. Most of the patients showed no clinical evidence of thyroid deficiency, although some had suggestive signs. In the beginning, desiccated thyroid (usually 2 grains [0.13 Gm.], U. S. P., a day) was prescribed without knowledge of the cholesterol value, when it was felt that thyroid might be of benefit. In most instances, the results of treatment were doubtful or negative in cases in which the cholesterol value was below 200 mg. One case of undoubted postoperative clinical myxedema showed a cholesterol value of 198 mg.; after treatment, the cholesterol fell to 120 mg. In prescribing thyroid, it has been my experience that most patients will discontinue it if it has not been helpful. On the other hand, it is not uncommon for them to discontinue it even if benefit has resulted, but they either will resume it on their own volition

or will agree that it produced improvement. It is largely by this means that results of the administration of thyroid have been evaluated in these postoperative cases.

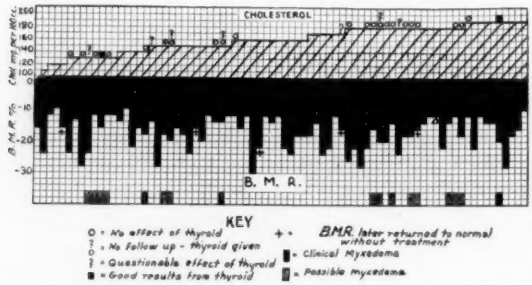

CHOLESTEROL
B. M. R.
KEY
0 = No effect of thyroid
1 = No follow up - thyroid given
? = Questionable effect of thyroid
■ = Good results from thyroid
+ = B.M.R. later returned to normal without treatment
■ = Clinical Myxedema
■ = Possible Myxedema

Chart 1.—Data on cases of postoperative thyroid disease with low metabolic rates and blood cholesterol of less than 200 mg. Note the infrequency of clinical myxedema as well as beneficial effects of the administration of thyroid.

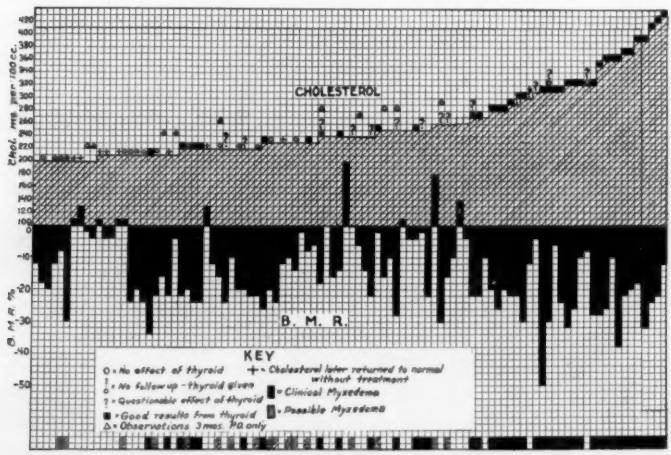

CHOLESTEROL
B. M. R.
KEY
0 = No effect of thyroid
1 = No follow up - thyroid given
? = Questionable effect of thyroid
■ = Good results from thyroid
Δ = Observations 3 mos. P.A. only
+ = Cholesterol later returned to normal without treatment
■ = Clinical Myxedema
■ = Possible Myxedema

Chart 2.—Data on cases of postoperative thyroid disease with cholesterol over 200 mg. regardless of the basal metabolic rate. Note the increasing frequency and severity of clinical myxedema as higher cholesterol values are reached. Note the variability of the basal metabolic rates which were observed after a night's stay in the hospital.

POSTOPERATIVE HYPERCHOLESTEREMIA WITH NORMAL OR LOW METABOLISM

In chart 2 are shown findings in eighty-nine unselected postoperative cases with a cholesterol value of 200 mg. or more. Some of the patients with high cholesterol values later showed normal values without treat-

ment. To be noted in chart 2 is the higher incidence of clinical myxedema as higher cholesterol values are reached, as well as the better results obtained from administering desiccated thyroid. The metabolic rates vary considerably, and some are above the normal average; these discrepancies may be due to emotional disturbances which occur from time to time. Although they can hardly be considered true basal metabolic rates, it did not seem desirable to omit them from the chart.

SUCCESSIVE CHANGES IN THE BLOOD CHOLESTEROL IN THE DEVELOPMENT OF POSTOPERATIVE MYXEDEMA

As stated in part II of this study,[18a] the blood cholesterol may be said to follow one of three courses after operation for hyperthyroidism. 1. It

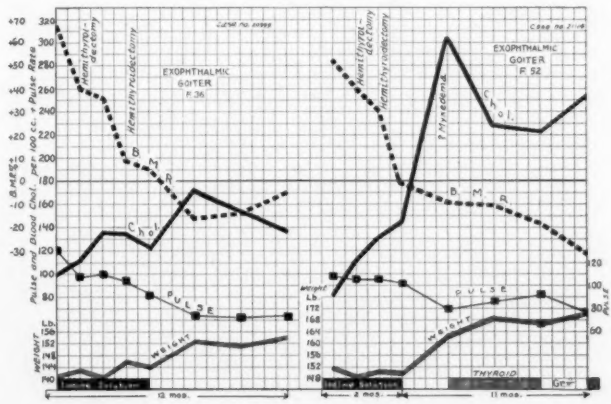
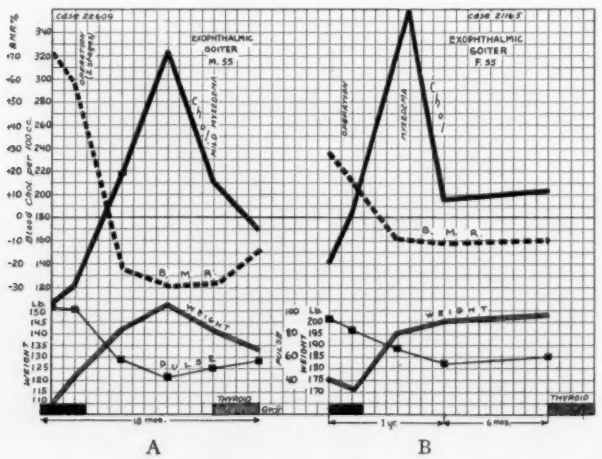


Chart 3.—*A*, data on a case of severe exophthalmic goiter; note the effect of a compound solution of iodine (represented by solid black) and two hemithyroidectomies. There was a postoperative low basal metabolic rate without hypercholesteremia. The basal metabolic rate returned to normal, and there was a slight drop in cholesterol at the end of nine months. *B*, the effect of a compound solution of iodine and two hemithyroidectomies in a case of severe exophthalmic goiter. There was postoperative hypercholesteremia without a low metabolic rate or clear-cut myxedema. Administration of desiccated thyroid lowered the cholesterol; the omission of thyroid for three months showed a rise in the cholesterol, an increase in weight, a drop in the basal metabolic rate and the pulse rate and a return of the symptoms. Administration of compound solution of iodine is indicated by solid black at the lower border of the chart.

18a. Hurxthal, L. M.: Blood Cholesterol in Thyroid Disease; II. Effect of Treatment, Arch. Int. Med. **52**:86 (July) 1933.

may return to normal and remain within the normal range (chart 3*A*). 2. It may rise above normal with or without clinical myxedema and subsequently fall within the normal range without treatment (charts 4*A*, 4*B* and 5*B*). 3. It may rise above normal and remain there, usually with the development of myxedema, unless reduced by the administration of thyroid (charts 3*B*, 5*A* and 6*B* and *C*).

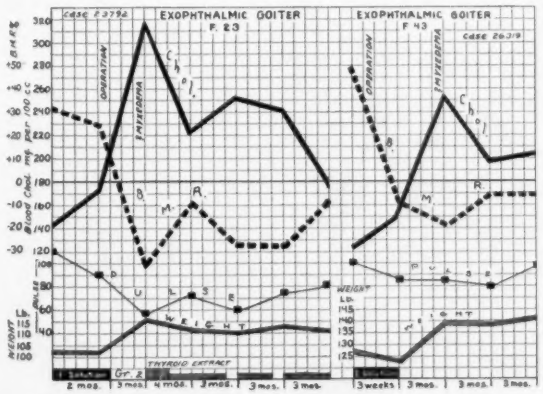
The effect of roentgen treatment over the thyroid is shown by the two cases illustrated in charts 6*A* and 7. In one case, roentgen therapy was given for a keloid scar six months after operation, by which time a temporary hypercholesteremia had subsided. Thereafter myxedema developed, and in view of the aforementioned events, it is reasonable



A B

Chart 4.—*A*, the effect of a compound solution of iodine on severe exophthalmic goiter before the first operation. Two hemithyroidectomies resulted, in three months, in a low basal metabolic rate and a cholesterol level of 220 mg. For a while there were no symptoms; three months later there were hypercholesteremia, a further drop in the basal metabolic rate and in the pulse rate and an increase in weight; there were no complaints other than a dry skin and an excessive gain in weight. Thyroid therapy was prescribed. When thyroid was not taken there was a spontaneous drop in cholesterol and in weight; after the thyroid was taken, a rise in the basal metabolic rate and pulse rate and a further drop in cholesterol and weight occurred. *B*, the effect of subtotal thyroidectomy on moderate exophthalmic goiter: postoperative hypercholesteremia without marked hypometabolism, and definite clinical myxedema of mild degree. No treatment was given. There were a normal range of cholesterol and a normal basal metabolic rate at the end of a year and eighteen months, and suggestive evidence of slight myxedema but marked improvement in well-being. Thyroid therapy was prescribed as a trial, with some (?) improvement, as reported by letter. Solid black indicates administration of compound solution of iodine.

to assume that thyroid deficiency resulted from the effect of the roentgen rays on the thyroid remnant. In the second case (chart 7), hypercholesteremia with mild but transient myxedema was produced when roentgen rays and compound solution of iodine were used. A cholesterol level of 575 mg. was found in another patient who had received a long series of roentgen treatments following operation for what was thought to be exophthalmic goiter. As the symptoms did not improve with roentgen therapy, she was referred to the Lahey Clinic for further operation. The basal metabolic rate was reported elsewhere as always above + 20. The patient continued to complain of palpitation and nervousness, although she felt cold and weak and presented a very dry skin. Thyroid was therefore tried for a period; this further increased



A B

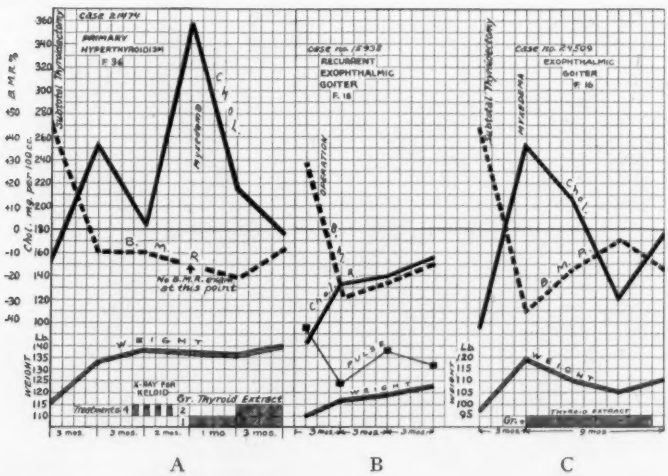
Chart 5.—*A*, effect of compound solution of iodine and operation on moderate exophthalmic goiter: postoperative hypercholesteremia, hypometabolism and borderline mxyedema. The effect of thyroid therapy is shown. Omission of thyroid for several weeks caused a rise in cholesterol and a drop in the basal metabolic rate. The continuation of thyroid and the omission again before the last observation maintained the cholesterol and the basal metabolic rate at the same level as on the previous omission, although physical signs were not clearcut. The symptoms were those of thyroid deficiency, and they were relieved by the administration of thyroid. *B*, data on a case of moderate exophthalmic goiter, in which operation was followed by hypercholesteremia and hypometabolism of moderate degree without clearcut myxedema. The treatment was purposely withheld; there were a return to normal range and an improvement in symptoms. Compound solution of iodine is indicated by solid black.

the nervousness and palpitation. It was therefore discontinued. The sensitiveness to cold and the dryness of the skin disappeared. When the patient was seen nine months later, there was no evidence of thyroid deficiency, although the thyroid pills had been stopped eight months before. The blood cholesterol at that time was 238 mg. Apparently the

thyroid had been temporarily depressed as the result of roentgen treatment and then had recovered. Basal metabolic studies were not obtained in this case.

CHRONIC THYROIDITIS

In part I of this study it was shown that the average cholesterol value for patients with chronic thyroiditis was above the normal average. Patients with frank myxedema were not included in this group. Not every patient with chronic thyroiditis will show a cholesterol value above the average, because there are two other factors which influence the blood cholesterol in this disease: (1) The element of infection, if it has not passed the active stage, tends to lower the cholesterol; (2) it is



A B C

Chart 6.—*A*, exophthalmic goiter. Subtotal thyroidectomy resulted in temporary postoperative hypercholesteremia, and roentgen therapy for the keloid scar caused by the incision was followed by the development of myxedema. Treatment with desiccated thyroid was instituted. *B*, recurrent exophthalmic goiter. The thyroid remnants were excised. Postoperatively there were a low basal metabolic rate, headache and amenorrhea (menstruation had been scanty and irregular for years). Administration of desiccated thyroid afforded no improvement. There was a gradual return of the metabolism to normal without hypercholesteremia. *C*, exophthalmic goiter. Subtotal thyroidectomy was followed by myxedema, low metabolism and hypercholesteremia. Thyroid extract was administered for eight and one-half months; it was omitted for two weeks before the last observation.

not uncommon for a mild hyperthyroidism to be present in the early stage of the disease. Postoperative myxedema is probably more likely to occur in chronic thyroiditis if operation is performed than in ordinary exophthalmic goiter. In fact, simply removing the isthmus for relief

of tracheal pressure may be followed by myxedema. The development of hypercholesteremia after operation in a case of this type, without previous hyperthyroidism, clearly demonstrates that it is the result of thyroid deficiency and substantiates the contention that hypercholesteremia following subtotal thyroidectomy for toxic goiter is due to thyroid deficiency rather than to the previous presence of increased thyroid activity such as has been described following hyperthyroidism induced with thyroid extract.[7b]

In one case of chronic thyroiditis which was seen since part I of this study was submitted, a cholesterol value of 680 mg. was found. Six months prior to admission, the patient had severe tonsillitis followed by soreness in the neck. Following this the patient became easily fatigued,

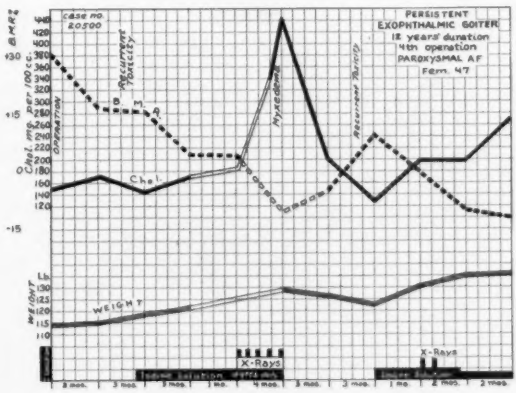


Chart 7.—Data on a case of persistent exophthalmic goiter of twelve years' duration at the time of the fourth operation; compound solution of iodine was not given for four months after the operation, at which time a recurrence took place and the solution was resumed. There were a drop in the basal metabolic rate and a rise in cholesterol; five roentgen treatments were given over the thyroid. Hypercholesteremia and mild myxedema (feeling of coldness, sleepiness and a dry skin) developed; toxicity recurred at the end of six months, with a drop in the cholesterol and a rise in the metabolic rate; administration of compound solution of iodine caused a drop in the basal metabolic rate and a rise in cholesterol; two more roentgen treatments caused a further drop in the basal metabolic rate but no change in the cholesterol. The patient is now well. The unshaded short lines in the chart indicate no observations; the lines are used merely to connect the preceding and the following observations. Solid black indicates compound solution of iodine.

gained weight and could carry on her work only with great effort. On examination, the thyroid was about three or four times its normal size and firm in consistency throughout. The appearance of the patient, the

character of the skin, and the complaints as related to myxedema were inconclusive. A diagnosis of myxedema could therefore not be definitely made. The first basal metabolic rate was plus one. This test could not be repeated at the time, so that it cannot be stated conclusively that this represented the true basal rate; yet there was no difficulty in taking the test, and the patient spent a quiet night in the hospital beforehand. However, as the likelihood of thyroid deficiency with chronic thyroiditis was known, she was given thyroid extract, 2 grains (0.13 Gm.), U. S. P., per day, before the report of the blood cholesterol was received. The results of treatment in her case have been so striking, and her appear-

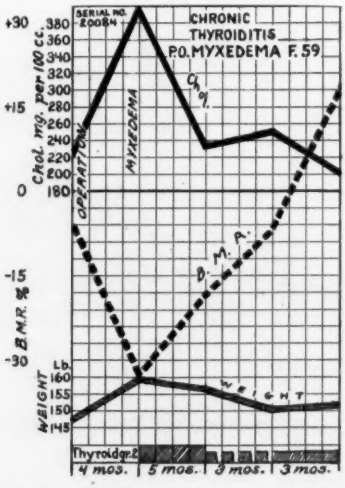


Chart 8.—Data on a case of chronic thyroiditis in which the cholesterol was above, and the basal metabolic rate below, the normal average. On the removal of the thyroid isthmus, myxedema developed. The effect of thyroid administration is shown. Irregular administration of thyroid resulted in a slight rise in cholesterol, with a return to the normal level when a smaller dose (1 grain [0.065 Gm.]) was given regularly. The cholesterol values in this case proved to be the most reliable laboratory guide in the treatment. The last metabolic rate particularly was the result of some emotional upset.

ance and behavior have changed so remarkably that the diagnosis of myxedema cannot be questioned.

Chart 8 shows observations on a patient with chronic thyroiditis who was operated on for relief of pressure. Only the thyroid isthmus was removed. In four months the patient returned with typical myxedema. Desiccated thyroid was then administered, with the usual relief. The cholesterol curve which displays a contour similar to that of the weight

curve is to be noted. The last basal metabolic rate is inconsistent with the cholesterol value and weight; it was probably caused by some emotional disturbance at the time of observation.

Of eight patients with chronic thyroiditis who were operated on and whose blood cholesterol was determined before operation, typical myxedema and hypercholesteremia of over 300 mg. developed in four. Of the remaining four patients, one showed no significant change in metabolic rate, cholesterol or physical condition (except a gain of 49 pounds [22.2 Kg.] in four months); another showed a lower metabolism and a slight rise in cholesterol but no obvious change in physical

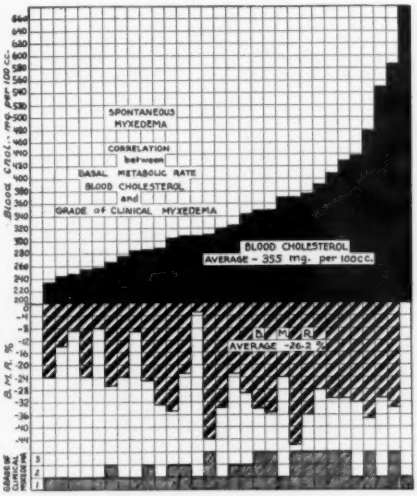
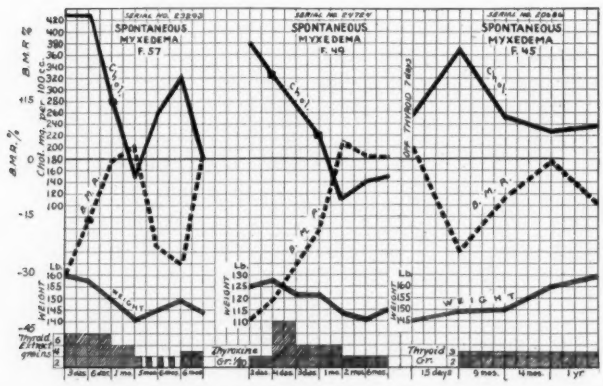

SPONTANEOUS MYXEDEMA
CORRELATION between BASAL METABOLIC RATE BLOOD CHOLESTEROL and GRADE OF CLINICAL MYXEDEMA
BLOOD CHOLESTEROL
AVERAGE - 355 mg. per 100cc.
B.M.R.
AVERAGE -26.2 %

Chart 9.—The findings in patients with myxedema before treatment was started and an estimate of the degree of clinical myxedema. In a general way, the greater the cholesterol and the lower the metabolism, the greater is the degree of myxedema. In several cases, and especially the last case, the first estimate of the degree of myxedema was erroneous, as judged from observations following treatment.

condition; a third, who probably had mild hyperthyroidism, showed a rise of from 189 to 248 mg. and a drop in metabolic rate of from + 15 to — 13 per cent without physical change; the fourth was distinctly toxic and showed a rise in cholesterol of from 181 to 305 mg. with a drop in metabolism of from + 35 to — 3 per cent and a gain of 15 pounds (6.8 Kg.) in weight. Up to the time of writing there was no evidence of myxedema. In five other patients with chronic thyroiditis who were operated on and in whom myxedema developed afterward, the blood cholesterol values were all more than 300 mg. (Determination of the blood cholesterol was not made before operation in these cases.)



A B C

Chart 10.—*A*, myxedema of many years' duration. Thyroid was administered, 6 grains (0.4 Gm.) a day for nine days; then the patient was discharged on a dosage of 4 grains (0.26 Gm.) a day. Too rapid administration proved disagreeable to the patient. Although the dose was reduced to 2 grains (0.13 Gm.) a day at the end of the month, the patient took this irregularly until finally, with the gradual increase of the dose from 2 to 3 grains (0.13 to 0.2 Gm.) a day, the patient returned, relieved of myxedema and in good condition, except that angina pectoris was present on exertion. The dose was reduced. This case illustrates the reciprocal relationship between metabolism and cholesterol. The percentage of elevation of the cholesterol as compared to the lowering of the basal metabolic rate was approximately in the ratio of 5:1. *B*, myxedema. Illustrating the rapid fall (similar to that in *A*) of cholesterol during a period of days and a rise in the basal metabolic rate on administration of thyroid. At the end of one month the dose of 4 grains (0.26 Gm.) of thyroid proved too much, and the dose was reduced to 2 grains (0.13 Gm.) for two months. This proved to be the optimum dose and was, therefore, continued for six months. Note the gain in weight, although the basal metabolic rate and the cholesterol remained the same. The ratio in percentage between the height of the cholesterol before treatment and the depression of the basal metabolic rate was approximately 3:1. *C*, myxedema. The patient discontinued thyroid therapy seven days before coming under my observation. The basal metabolic rate and the cholesterol were within the normal range. Thyroid was further discontinued for fifteen days, with a short drop in the basal metabolic rate and a rise in cholesterol. Three grains (0.2 Gm.) of thyroid were then administered. The initial drop in weight was not recorded, as the patient left the hospital, but thereafter a gain in weight continued in spite of the improvement in the basal metabolic rate and the cholesterol. The ratio here between the height of the cholesterol and the lowering of the basal metabolic rate in per cent was approximately 4:1.

SPONTANEOUS MYXEDEMA

Thirty additional cases of spontaneous myxedema in which studies of the cholesterol were made have been observed. These are graphically shown in chart 9. Five of the patients had a metabolic rate between 0 and —12 per cent. I was able to repeat the tests in three instances, in two of which there was a 5 per cent decrease on the second day in the hospital and in another of which there was a 3 per cent decrease. It is possible that in these cases a lower rate could have been obtained, but since no difficulty was encountered by the patients in taking the test, it is only a possibility. Although it may be doubted that these are true basal rates, it is important to point out that such readings are obtained even under most favorable conditions and therefore may be misleading. It is interesting to note, how-

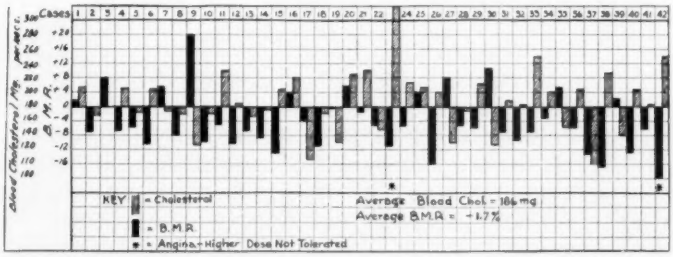


Chart 11.—The findings in forty-two cases of myxedema (operative and spontaneous) when optimum doses of desiccated thyroid or thyroxine were being administered. The value of the cholesterol or the basal metabolic rate is shown by polygons projected above or below the normal average base line. If the polygons for cholesterol were represented in percentage deviation from normal, they would be approximately twice their present size. It is to be noted, however, that the cholesterol of the majority is below 220 mg.

ever, that in one hundred and twenty cases of hypothyroidism, Rowe and Lawrence [19] found a basal metabolic rate of —10 or less in every instance.

RESULTS OF TREATMENT AND THE BEHAVIOR OF THE BLOOD CHOLESTEROL IN SPONTANEOUS MYXEDEMA

In chart 10 is shown the course following treatment in three cases, in one of which thyroid was given and then taken irregularly, in another of which thyroid was omitted when the patient had been adequately treated, and then resumed and in a third of which thyroid was continued

19. Lawrence, C. H., and Rowe, A. W.: Studies on the Endocrine Gland: III. The Thyroid, Endocrinology **12**:377 (July-Aug.) 1928.

without interruption. The rapidity with which the metabolic rate and the cholesterol can be altered in a few days is to be noted also. (Rapid treatment, however, should be discouraged, for, although effects of thyroid may be noted more quickly, it is doubtful if time or added benefit is gained in the long run. Starting treatment on the average daily ration will produce the desired results without the disturbing symptoms occasionally seen when large doses are given.)

THE OPTIMUM RESULT IN RELATION TO THE BLOOD CHOLESTEROL AND BASAL METABOLIC RATE

In chart 11 are shown the cholesterol values in relation to the metabolic rate when the patient was considered to be on the proper ration of thyroid. Two cases depart considerably from the average; in these, angina developed on every attempt to increase the dose. The averages for the group show normal values.

CRETINISM

The blood cholesterol was studied in three cretins. One had been adequately treated, another had received inadequate treatment, and a third had been suspected of cretinism and had received small doses of thyroid, without benefit. The blood cholesterol was over 300 mg. in all three patients when they were not receiving thyroid. In the third case, the determination of the blood cholesterol was of great value in diag-

TABLE 2.—*Effect of Thyroid on Cholesterol in a Cretin*

Age	Cholesterol, Mg. per 100 Cc.	Weight, Pounds	Thyroid, Grains	Time, Weeks	Result
21 months	370	28.0	1		
	130	23.5	1	3	Improved
	121	23.5	1	6	Improved

nosis. The child had been observed in one hospital and discharged with the diagnosis of questionable cretinism. Because inadequate doses of thyroid had not produced beneficial results, the child was taken to several clinics, at which it was stated positively that the child was not a cretin. On first examination, the child displayed rather coarse features, but the skin was very soft, and the hair was fine and not brittle. The blood cholesterol was found to be 370 mg., and thyroid was tried in larger doses, following which remarkable clinical improvement occurred.

HYPERCHOLESTEREMIA IN DIAGNOSIS

It is obvious from what has been written in this report that when hypercholesteremia is found, except, of course, in diabetes mellitus, nephrosis and obstruction of the common duct, it is considered as possibly of thyroid origin. In patients with mental disorders, hypercho-

lesteremia has been reported by several observers.[20] Duncan [14g] tried thyroid extract in one patient with hypercholesteremia and dementia praecox. He described the patient as subthyroidic, thus inferring that typical myxedema was not present. The usual fall in cholesterol took place, and the patient became normal. When the administration of thyroid ceased, all of the symptoms returned, and hypercholesteremia again took place. Another of Duncan's patients with hypercholesteremia of less extent showed no improvement. In one case which I observed, the chief complaint was aural hallucinations. Examination suggested mild myxedema. The basal metabolic rate was determined, which was —22 per cent. In this patient, who was first seen over four years ago, the cholesterol value was not determined until recently, when the patient stopped taking thyroid for several weeks, at which time hallucinations again returned and hypercholesteremia was present. Administration of thyroxine was resumed, and a return to normal took place within a few days. Experience with two other patients suffering from mental depression and hypercholesteremia without evidence of myxedema, and with patients who have definite myxedema with mental disturbances of various types has suggested that a therapeutic trial is indicated in any mental case with hypercholesteremia, regardless of the metabolic rate, and that hypercholesteremia may be a more rational indication of thyroid deficiency in certain instances than a low metabolic rate per se.

The application of such a therapeutic trial of thyroid to other conditions is worthy of consideration. In the case cited earlier, in which chronic thyroiditis and a cholesterol value of 680 mg. were present, five physicians saw the patient, but the possibility of myxedema did not occur to them. Obesity and fatigue from overwork had been the usual diagnoses. Furthermore, the basal metabolic rate obtained was normal. Here, then, was a case of obesity of thyroid origin in which the diagnosis would not have been made in five of six instances without the strong possibility suggested by the hypercholesteremia and the presence of a thyroid gland characteristic of chronic thyroiditis.

Another patient recently came to the clinic with the complaint of goiter and renal disease. Moderate hypertension was present, the nonprotein nitrogen was above normal, albuminuria was marked, and the specific gravity of the urine was fixed. The basal metabolic rate was normal on three occasions. The appearance of the patient was consistent with chronic nephritis or mild myxedema. There was no pitting edema present. The blood cholesterol was over 400 mg. The serum protein was normal. On receiving thyroid extract the patient showed a remarkable improvement; the nodules in the thyroid disappeared, and the nonprotein nitrogen became lower. (This case will be reported in detail at a later date.) The condition could easily have passed unnoticed, with only

20. Schube,[14b] Duncan [14c] and Grabfield.[14e]

a diagnosis of chronic nephritis and without the great benefit resulting from the knowledge that myxedema was the chief cause of her complaints.

Pernicious anemia may occur in patients with myxedema.[21] One of the patients included in this study complained of inability to lose weight and difficulty in walking. She had taken inadequate amounts of liver on prescription before admission. The appearance of the patient did not suggest myxedema. The skin showed a yellowish tint and the cheeks were pink. The skin was soft and smooth, and the patient perspired and had no sensation of coldness. The last two points I wish to emphasize for they were affirmed again and again by the patient and her sister. The texture of the skin was striking in its fineness. There was no free hydrochloric acid found in an aspirated test meal. The red cell count and the hemoglobin were subnormal but, it was felt, not diagnostic because of previous liver therapy. Vibratory sense as indicated by the tuning fork was diminished in both legs. The reflexes were normal. Believing that further intensive liver therapy was indicated, liver extract was given intramuscularly three times a week, and approximately ½ pound (0.2 Kg.) of liver was eaten daily by the patient. At the end of one month, there was no change; the condition of the blood remained stationary. Only one clue to the possibility of myxedema was furnished by the patient's sister, after reflection over a question put to her, namely, that the patient talked a little more slowly during the past few years than previously. A specimen of blood was taken to determine the cholesterol value, which was 535 mg. The basal metabolic rate was then found to be — 30 per cent; had this not been low, I feel sure that the true diagnosis would have been passed by. Desiccated thyroid has completely changed the patient's condition, and her true normal condition can now be seen in striking contrast to her previous state. Apparently the condition had come on so gradually that the sister with whom she lived was unaware of it.

In seventeen cases in which the blood cholesterol was over 250 mg. classification has been difficult. In seven of these cases found after operation for toxic goiter, three patients have not been able to return for further study. The other four have been observed over periods of one or two years, and hypercholesteremia persists with normal basal metabolic rates (above — 10 per cent). No evidence of myxedema was found in three patients, and only suggestive evidence in one. All of the patients feel well. Two are excessively overweight and are taking thyroid, without toxic symptoms, but with loss of weight and reduction in the blood cholesterol (table 3).

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21. Means, J. H.; Lerman, J., and Castle, W. R.: The Coexistence of Myxedema and Pernicious Anaemia, New England J. Med. **204**:246 (Feb. 5) 1930.

TABLE 3.—*Effect of Administration of Thyroid on Postoperative Hypercholesteremia Without Evident Myxedema*

Date	Basal Metabolic Rate, per Cent	Cholesterol, Mg. per 100 Cc.	Pulse Rate	Weight, Pounds	Desiccated Thyroid, Grains per Day	Comment
			Woman, Aged 54 (19312): Toxic Adenomatous Goiter			
12/ 5/30	+30	...	100	187	..	Subtotal thyroidectomy
9/22/31	— 4	307	80	202	..	No complaints
12/17/31	+ 3	312	80	219		
5/ 2/32	+ 5	312	80	209	..	Weight reduced by diet
1/ 4/33	....	308	90	219½	2	Thyroid started; no diet
1/18/33	....	268	84	210	3	Thyroid increased
5/13/33	+11	245	92	202	3	Feels better; loss of 17½ pounds with thyroid therapy
			Woman, Age 21 (18954): Exophthalmic Goiter			
11/ 6/30	+85	...	120	126	..	Very toxic; subtotal thyroidectomy
11/21/31	+ 7	312	80	150	..	Went through pregnancy
12/15/31	....	397	..	157	..	No complaints; periods irregular
11/21/32	+12	329	98	163	..	No complaints
1/ 4/33	....	342	90	163	2	Thyroid started
2/ 4/33	....	297	88	157	3	Thyroid increased to 3 grains but stopped for a while, then resumed; hence gain in weight on 4/25/33
4/25/33	....	258	100	164	4	Periods regular and increased in amount; feels "peppier"; thyroid increased
5/15/33	+45	...	128	157	4	Thyroid reduced

TABLE 4.—*Results of Thyroid Therapy in Seven Patients not Operated on or Showing no Changes in the Thyroid*

Number	Clinical Impression	Complaint or Other Diagnosis	Basal Metabolic Rate	Cholesterol	Dose, Grains	Results
22562	Mild myxedema suspected	Fibroid uterus; fatigue; obesity	—18	280 (225)*	2	Excellent result
26671	Accidental finding	Constipation; "bloat"; obesity; hypertension	—15	272	2	Anginal symptoms developed; thyroid therapy stopped (report by mail)
23007	Accidental finding	Depression; obesity	— 9	260 (226)*	2	Not depressed when taking thyroid
27618	Mild myxedema suspected	Angina pectoris; obesity	....	294	1	Symptoms worse on 1 grain a day (stopped)
27262	Mild myxedema suspected	Peripheral vascular disease; anemia; fatigue	— 8	342 (216)*	2	No definite improvement
21821	Said to have myxedema	Constipation; thyroid stopped 2 weeks before	—15	284	0	No thyroid taken for 1 year; feels fine (report by mail)
31081	Obesity	Obesity; coldness	— 3	272	2	Excellent result

* This estimate was made after administration of thyroid.

Two other cases in this group of seventeen cases in which the blood cholesterol was over 250 mg. were found following removal of a nontoxic goiter. There were no complaints and no evidence of thyroid deficiency. In another case the patient showed a cholesterol value of 305 mg. before operation and of 336 mg. three months after operation. The patient stated that she had always felt cold and tired. Her skin was dry but otherwise displayed no evidence of thyroid deficiency. Thyroid was prescribed, and the patient wrote that although she felt much better when taking it, she became depressed and discontinued it. The remaining seven patients showed no changes in the thyroid and had not been operated on. They are listed with the results of thyroid therapy in table 4.

It is well to point out that this list would have been larger if I had included in it cases in which the initial diagnosis was distinctly in question, yet which were undoubtedly cases of myxedema, as proved by the striking results of the administration of thyroid.

Hypothyroidism without myxedema, amyxedemic thyroid failure and primary thyroid failure are terms which have been used to express in certain cases the combination of various symptoms and hypometabolism. Undoubtedly some of these are cases of thyroid deficiency, but it is also possible that some are not. It seems reasonable to conclude, on the basis of these studies, that thyroid failure always gives rise to myxedema and a rise in the cholesterol, but that the myxedema may be unrecognized because of the lack of characteristic physical findings, and can therefore rightly be termed imperceptible myxedema. Lawrence and Rowe [19] demonstrated an initial loss of weight in the case which they described as one of amyxedemic thyroid failure with a subsequent gain in weight. This is a common observation in clinical myxedema. This initial loss of weight in the atypical case, it would seem, is due to the loss of water from concealed myxedema. An analogy may be said to occur in congestive heart failure when occasionally no perceptible edema can be demonstrated, yet in which a masked diuresis can be produced by a diuretic. An occasional case with obvious myxedema in which the cholesterol may be considered within the upper limits of normal may be found, yet this does not vitiate the statement that hypercholesteremia is characteristic of thyroid deficiency, because for a certain person the high normal value may well represent an increase of 100 per cent over his normal level.

CONCLUSIONS

1. Postoperative myxedema is accompanied by hypercholesteremia.

2. Subtotal thyroidectomy may be followed by hypercholesteremia without clinical myxedema. This is interpreted as a transient thyroid deficiency.

3. Subtotal thyroidectomy may be followed by low metabolic rates, without hypercholesteremia. In these cases myxedema is seldom found.

4. Roentgen therapy can produce transient hypercholesteremia with or without clinical myxedema.

5. Removal of part of a thyroid gland affected by chronic thyroiditis may be followed by hypercholesteremia and myxedema.

6. Thyroid deficiency produces myxedema and hypercholesteremia, but at times myxedema may be clinically imperceptible.

7. Hypercholesteremia, when not explainable on any other basis, may be considered as possibly of thyroid origin, and is a rational indication for thyroid administration.

8. The finding of hypercholesteremia, in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low metabolic rate. Finding both renders the possibility of thyroid deficiency extremely likely.

9. The relationship between the blood cholesterol and the basal metabolism is usually reciprocal when they undergo change as the result of variations in the activity of the thyroid gland or thyroid substance in the body.

10. The blood cholesterol provides another variable which may be used as a guide in the treatment of thyroid disease.

Miss Bessie A. White, of the New England Baptist Hospital, collected many of the specimens of blood, and Miss Hazel M. Hunt, director of the chemical laboratories of the New England Deaconess Hospital, supervised the many analyses of the blood.

CEREBROSPINAL FLUID PRESSURE AND VENOUS PRESSURE IN CARDIAC FAILURE

AND THE EFFECT OF SPINAL DRAINAGE IN THE TREATMENT OF CARDIAC DECOMPENSATION

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That the venous pressure is elevated in persons with cardiac failure has been shown by a number of observers. Eyster and Middleton [1] and also Clark [2] clearly demonstrated by the indirect method of measurement that the venous pressure is an accurate guide to the course and prognosis in cardiac disease. A rising or persistently elevated venous pressure was found to offer a grave prognosis, while a falling venous pressure was observed to run parallel to the degree of improvement of the clinical condition of the patient. In studying venous pressure in cardiac failure and numerous other conditions, Harrison,[3] using the direct method, reached the same conclusion. He found that the so-called average normal pressure determined by this method was about the same as that reported for the indirect method used by Eyster.[4a]

It is well known that when the Queckenstedt test is performed pressure on the internal jugular vein is immediately followed by a rise in the cerebrospinal fluid pressure, provided there is no block. It occurred to me that perhaps persons with cardiac decompensation who show an elevation of venous pressure might likewise show an increase in cerebrospinal fluid pressure. Accordingly lumbar puncture was performed on a patient with marked congestive heart failure, and the pressure of the fluid was found to be greatly increased. Further studies were therefore carried out.

From the Department of Internal Medicine, Emory University School of Medicine, and Grady Memorial Hospital (colored unit).

1. Eyster, J. A. E., and Middleton, W. S.: Clinical Studies on Venous Pressure, Arch. Int. Med. **34**:228 (May) 1924.

2. Clark, A.: A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, Arch. Int. Med. **16**:587 (Oct.) 1915.

3. Harrison, W. G., Jr.: Clinical Studies in Venous Pressure, to be published.

4. Eyster, J. A. E.: (*a*) Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929; (*b*) Clinical and Experimental Observations upon Cheyne-Stokes' Respirations, J. Exper. Med. **8**:565, 1906.

SPINAL FLUID AND VENOUS PRESSURES IN CONDITIONS OTHER THAN CONGESTIVE HEART FAILURE

The spinal fluid and venous pressures were studied in ten persons, none of whom had any evidence of congestive heart failure. In all instances the patients were resting quietly in bed. The spinal fluid pressure was recorded by means of the Ayer water manometer when lumbar puncture was performed, with the patient lying on his side in the prone position with his head on two flat pillows. The venous pressure in millimeters of water was determined by the direct method of Moritz and Tabora,[5] the patient lying flat on his back in the prone position with his head on two pillows. In determining the venous pressure care was exercised to make certain that the zero reading of the water

TABLE 1.—*Spinal Fluid Pressure and Venous Pressure in Ten Control Patients Having No Evidence of Congestive Heart Failure*

Patient	Condition	Spinal Fluid Pressure, Mm. of Water	Venous Pressure, Mm. of Water	Ratio
1. E. R.	Neurosyphilis	105.0	70.0	1.5
2. F. B.	Acute gastritis	80.0	65.0	1.2
3. T. T.	Arsphenamine hepatitis	110.0	60.0	1.8
4. C. C.	Fibrinous pleurisy	150.0	75.0	2.0
5. O. L.	Chronic nephritis	150.0	75.0	2.0
6. O. H.	Duodenal ulcer	100.0	75.0	1.3
7. H. H.	Chronic lymphatic leukemia	90.0	45.0	2.0
8. W. M.	Osteomyelitis	80.0	40.0	2.0
9. M. B.	Miliary tuberculosis	110.0	65.0	1.6
10. A. N.	Hypertension	90.0	75.0	1.6
	Average	106.5	64.5	1.6

manometer, the vein and the right auricle were all at the same level. At least three readings were taken each time. Most of the observations were made in the afternoon. The venous pressure was usually determined first, and this was followed immediately by the spinal fluid pressure readings.

In all instances the spinal fluid pressure and the venous pressure were within the normal limits (table 1). It was found that there was a definite ratio between the spinal fluid pressure and venous pressure. Although this varied from 1:2 to 2:0, it was fairly constant and averaged 1.6. Undoubtedly, if a larger series of cases had been studied, this ratio would have been lower in some cases and higher in others, but in general this may be considered as the average normal ratio.

5. Moritz, F., and Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exacter zu bestimmen, Deutsches Arch. f. klin. Med. **98**: 475, 1910.

SPINAL FLUID AND VENOUS PRESSURES IN CONGESTIVE HEART FAILURE

The spinal fluid pressure and venous pressure were next similarly studied in a group of ten patients with congestive heart failure, all of whom had either syphilitic aortic insufficiency or hypertensive heart disease (table 2). It was found that all the patients with increased venous pressure had an increase in spinal fluid pressure. In those who showed a marked increase in venous pressure the spinal fluid pressure was also greatly increased. The higher the venous pressure the higher was the spinal fluid pressure observed. The ratio between the spinal fluid pressure and venous pressure ranged from 1:4 to 1:8, and the average was 1:6. This is the same average ratio reported in the

TABLE 2.—*Spinal Fluid Pressure and Venous Pressure in Ten Patients with Congestive Heart Failure*

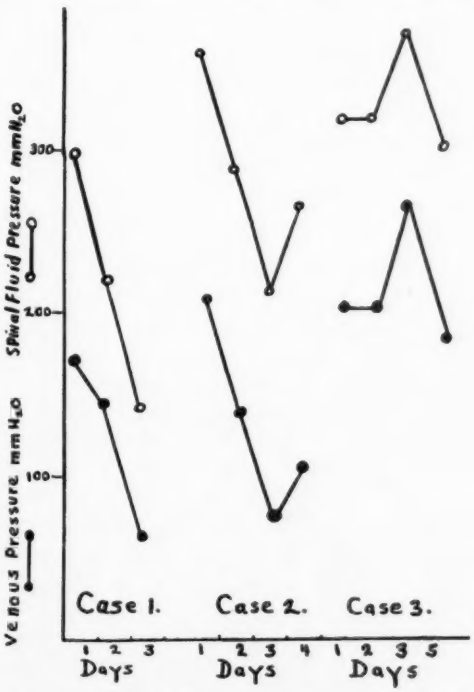
Patient	Condition	Spinal Fluid Pressure, Mm. of Water	Venous Pressure, Mm. of Water	Ratio
1. R. S.	Hypertensive heart disease	300.0	210.0	1.4
2. T. W.	Hypertensive heart disease	420.0	275.0	1.5
3. J. D.	Hypertensive heart disease	520.0	305.0	1.7
4. C. J.	Hypertensive heart disease	380.0	255.0	1.4
5. C. P.	Syphilitic aortic insufficiency	465.0	295.0	1.5
6. J. H.	Syphilitic aortic insufficiency	365.0	210.0	1.7
7. W. A.	Hypertensive heart disease	415.0	225.0	1.8
8. W. J.	Hypertensive heart disease	475.0	270.0	1.7
9. E. R.	Hypertensive heart disease	455.0	270.0	1.6
10. D. H.	Syphilitic aortic insufficiency	360.0	190.0	1.8
	Average	415.5	250.5	1.6

control group (table 1), and it can be seen that in general this ratio tends to remain about the same. The average venous pressure in the group of patients with cardiac failure was 250.5, as compared with 64.5 in the control group, and the average spinal fluid pressure in the group with cardiac disease was 415.5, as compared with 106.5 in the control group. The spinal fluid pressure and venous pressure in the group with cardiac failure were nearly four times as great as in the control group. Thus, the cerebrospinal fluid pressure is markedly increased in patients with congestive heart failure.

EFFECT OF CLINICAL IMPROVEMENT ON THE SPINAL FLUID AND VENOUS PRESSURES

The next series of observations consisted in following the changes in cerebrospinal fluid pressure and venous pressure as the patient with cardiac failure experienced clinical improvement under treatment (chart,

cases 1, 2 and 3). It can be seen that the changes in the spinal fluid pressure ran parallel to the changes in the venous pressure. When the venous pressure fell the spinal fluid pressure likewise fell. When the venous pressure rose the spinal fluid pressure rose. In case 1, in which the condition was syphilitic aortic insufficiency, both pressures fell to normal as the patient improved. In case 2, in which the condition was also syphilitic aortic insufficiency, both pressures fell nearly to normal



This chart shows the effect of clinical improvement on the spinal fluid pressure and venous pressure. Note the parallel course of the two pressures in three patients with congestive heart failure.

but later rose slightly. At this point the patient left the hospital, and no more observations were made on her. In case 3, in which the condition was hypertensive heart disease, there was also a parallel rise and fall of the two pressures in a patient who at first did not respond well to treatment. These three cases show that, except for slight variations, the spinal fluid pressure runs closely parallel to the venous pressure as the patient with congestive heart failure regains compensation.

EFFECT OF SPINAL DRAINAGE ON DYSPNEA AND VENOUS PRESSURE IN CONGESTIVE HEART FAILURE

Various drugs have been used to lower the venous pressure,[6] but the results have not been very satisfactory. The striking effect of venesection in lowering the venous pressure in patients with cardiac failure has been repeatedly demonstrated, and it occurred to me that since the spinal fluid pressure was markedly increased in these patients spinal drainage might prove of some benefit. In thirteen instances, therefore, patients who had either syphilitic aortic insufficiency or hypertensive heart disease were subjected to spinal drainage, and the effect on dyspnea, as stated by the patient, and on the venous pressure was

TABLE 3.—*Effect of Spinal Drainage on the Spinal Fluid and Venous Pressures in Thirteen Patients with Congestive Heart Failure*

Patient	Condition	Amount of Spinal Fluid Removed, Cc.	Spinal Fluid Pressure, Mm. of Water		Venous Pressure, Mm. of Water	
			Before Removal	After Removal	Before Removal	After Removal
	Cases in Which a Fall in Venous Pressure Occurred					
1. T. W.	Hypertensive heart disease.....	35	420.0	110.0	275.0	200.0
2. C. W.	Syphilitic aortic insufficiency....	20	375.0	150.0	285.0	260.0
3. J. H.	Syphilitic aortic insufficiency....	25	365.0	95.0	210.0	175.0
4. W. A.	Hypertensive heart disease.....	20	375.0	150.0	265.0	245.0
5. C. W.	Syphilitic aortic insufficiency....	20	250.0	150.0	130.0	100.0
6. W. A.	Hypertensive heart disease.....	20	320.0	120.0	210.0	165.0
7. W. B.	Syphilitic aortic insufficiency....	30	370.0	120.0	165.0	125.0
8. R. S.	Hypertensive heart disease.....	30	300.0	100.0	210.0	155.0
	Average.....	25	346.8	124.3	218.7	178.1
	Average fall in venous pressure	..	.....	.....	.....	40.6
	Cases in Which No Fall in Venous Pressure Occurred					
9. J. C.	Hypertensive heart disease.....	25	350	125	145	185
10. J. D.	Hypertensive heart disease.....	65	520	170	305	390
11. W. A.	Hypertensive heart disease.....	20	300	90	185	185
12. D. H.	Syphilitic aortic insufficiency....	20	360	150	190	190
13. R. S.	Hypertensive heart disease.....	40	290	20	120	120

studied. In one patient, W. A., drainage was carried out three different times, and the readings were listed separately in table 3. In another patient, R. S., drainage was carried out twice, and the readings were listed separately. The venous pressure was recorded in the manner previously stated immediately before and after drainage. The amount of spinal fluid removed varied (table 3).

In eight instances the venous pressure fell following spinal drainage. The fall was marked in some cases; in others it was not so pronounced. In none of the cases did the venous pressure fall as much as the spinal fluid pressure. At this point, therefore, the ratio between the spinal fluid pressure and the venous pressure was obviously not the same as before. The average fall in venous pressure in the eight instances was

6. Capps, J. A., and Matthews, S. A.: Venous Blood Pressure as Influenced by the Drugs Employed in Cardiovascular Therapy, J. A. M. A. **61**:388 (Aug. 9) 1913.

40.6 mm. of water. In two cases the venous pressure rose instead of fell. In three cases there was no change in the venous pressure. Most of the patients stated, however, that they were able to breathe better following spinal drainage. This seemed to be true also for some of those who had experienced no fall in venous pressure. Many of the patients were able to breathe with nearly as much comfort lying down as they previously had done sitting up. In the majority of the cases this effect appeared to be a temporary improvement.

EFFECT OF POSTURE ON THE VENOUS, SPINAL FLUID AND CISTERNAL PRESSURES

The improvement of the patients with cardiac disease after spinal drainage suggested further observations that might help to explain why patients with this disease breathe better in the sitting than in the prone position. It is well known that in normal persons the lumbar spinal fluid pressure is much greater in the sitting position than in the prone position. It seemed to me that the cisternal pressure should be lower in this position. Indeed, this pressure has been reported to be below zero in the sitting position in the normal person.[7] The observations of Weed [8] on animals showed definitely this difference in pressure in the two positions. On the other hand, I know of no observations on the cisternal pressure in congestive heart failure. While studying the spinal fluid in a patient with syphilis and while attempting to give a patient with cardiac failure some relief by spinal drainage, an opportunity was offered to measure the cisternal pressure in the two patients in the sitting and prone positions.

The venous pressure, lumbar spinal fluid pressure and cisternal pressure in the sitting position were studied in the patient with syphilis. This subject was used as the normal or control. He was then placed in the prone position on his side, and the observations were repeated. The venous pressure was recorded in the prone position with the patient on his back, as was previously stated. A specially constructed U manometer filled with physiologic solution of sodium chloride was used to record the cisternal pressure. The same procedure was then carried out on a patient with hypertensive heart disease and congestive failure. Observations were obtained on only one control patient and one patient with cardiac disease. Weed, Flexner and Clark [9] have shown that the

7. Ayer, J. B., in The Human Cerebrospinal Fluid. An Investigation of the Most Recent Advances, as Reported by the Association for Research in Nervous and Mental Disease, New York, Paul B. Hoeber, Inc., 1926, p. 159.

8. Weed, L. H.: Positional Adjustments of the Pressure of the Cerebrospinal Fluid, Physiol. Rev. **13**:80, 1933.

9. Weed, L. H.; Flexner, L. B., and Clark, J. B.: The Effect of Dislocation of Cerebrospinal Fluid upon Its Pressure, Am. J. Physiol. **100**:246, 1932.

fall in cerebrospinal fluid pressure is proportional to the amount of fluid removed. This source of error, however, is small in these determinations, and for purposes of comparison it may be considered negligible, since it is the difference in the pressure readings in the two positions which is of special concern. Table 4 shows the results of the readings.

The venous pressure and lumbar spinal fluid pressure in both the control patient and the patient with cardiac disease were much greater in the sitting than in the prone position. The cisternal pressure, on the other hand, was much lower in each person in the sitting than in the prone position. In the patient with cardiac failure, however, the cisternal pressure was higher in the sitting position than in the control patient, and the difference in the cisternal pressure in the two positions was greater in the patient with cardiac disease than in the control. Although the difference between the cisternal pressure in the two

TABLE 4.—*Differences in the Venous, Spinal Fluid and Cisternal Pressures in One Control Patient and One Patient with Congestive Heart Failure in the Prone and Sitting Positions*

	Control Patient			Patient with Cardiac Failure		
	Prone Position	Sitting Position	Difference	Prone Position	Sitting Position	Difference
Venous pressure, mm. of water.....	50	70	20	310	355	45
Spinal fluid pressure, mm. of water..	125	430	305	400	680	280
Cisternal pressure, mm. of water....	102	15	87	355	100	255

positions was considerable in the control patient, in the patient with cardiac disease this difference was enormous—255 mm. of water. Thus, the cisternal pressure and consequently the pressure in the region of the medulla are markedly decreased when the patient changes from the prone to the sitting position, and this is more pronounced in the patient with cardiac failure than in the normal person. This observation suggests one reason why spinal drainage helps patients with congestive heart failure. It seems that drainage is partly equivalent to changing to a sitting position. It also suggests one important reason why patients with this condition breathe better in the sitting than in the prone position and hence furnishes considerable information on orthopnea.

COMMENT

The close relationship that exists between spinal fluid pressure and cerebral venous pressure has been definitely established.[10] According

10. Hill: Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, 1896.

to Weed and Hughson,[11] alterations in the intracranial venous pressure effect changes in the pressure of the cerebrospinal fluid in the same direction but not to the same extent. Curiously enough, the spinal fluid pressure has not been thoroughly investigated in heart failure. In spinal drainage in a patient with cardiac disease one should guard against removing the spinal fluid too rapidly or taking out too much at once from a very ill patient with a markedly elevated venous pressure. Some of these patients complain of headache after drainage; hence, caution is advised in using this method of treatment.

A number of facts must yet be learned about spinal drainage in heart failure. In the first place, if a patient experiences improvement one should know how long this improvement will last. The effect usually appears to be temporary. One should know also how much fluid to remove. Unquestionably these factors vary with the clinical condition of the patient. The mild cases will not need drainage. The effect of hypertonic solutions, such as dextrose and magnesium sulphate, should be studied and may prove to be of value. The mechanism of clinical improvement and fall in venous pressure following spinal drainage in some of these patients has yet to be investigated, and studies are now being carried out along these lines. Before this method of treatment can be of great value therapeutically, the study of a larger series of cases is advisable.

In studying the changes in pressure observed in the sitting and prone positions in patients with cardiac disease, one has to consider the much discussed cause of orthopnea. That the vital capacity is increased in the sitting position, as compared with the prone position, has been definitely shown to be true.[12] Undoubtedly this is one of the major causes of orthopnea. Ernstene and Blumgart [13] thought that orthopnea could be explained largely by the increased blood supply to the respiratory center as a result of the lowering of cerebral venous pressure when the patient assumed the erect position. The observations here reported tend to show that one reason why patients with cardiac disease breathe better in the sitting than in the prone position is that there is marked decrease in cisternal pressure and hence decrease in pressure on the medulla. Whether this is due to a direct effect of the pressure of the fluid, to an accompanying change in cerebral venous pressure or to some

11. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by the Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **58**:101, 1921.

12. Christie, C. D., and Beams, A. J.: Orthopnea, Arch. Int. Med. **31**:85 (Jan.) 1923.

13. Ernstene, A. C., and Blumgart, H. L.: Orthopnea: Its Relation to the Increased Venous Pressure of Myocardial Failure, Arch. Int. Med. **45**:593 (April) 1930.

indirect effect has yet to be ascertained. Certainly it appears that, in addition to the increased vital capacity, the decreased cisternal pressure is an important factor in producing the relief from dyspnea obtained in the sitting position. The studies here reported likewise explain Ernstene and Blumgart's observations that, although the vital capacity of the patient with cardiac disease is not changed by flexion of the head, patients with this condition breathe better in this position than in the absolute prone position.

Eyster [4b] has shown that an increase in intracranial pressure will produce Cheyne-Stokes' breathing if waves of blood pressure are called forth to such an extent that the intracranial pressure alternately rises and falls above the level of arterial pressure. He thought that this might explain the cause of Cheyne-Stokes' respiration in some clinical conditions in which there is increased intracranial pressure, but not in cardiac failure. Since it is now proved that in congestive heart failure the intracranial pressure is markedly increased, the Cheyne-Stokes' respiration in some patients with cardiac disease may be explained in a similar manner. In other words, the increase in intracranial pressure may be the initial stimulus which calls forth Cheyne-Stokes' respiration in persons with cardiac failure. Further studies, which are now in progress, must be carried out before this can be shown to be true.

It has been shown by Cushing [14] that if the cerebrospinal fluid pressure rises to a certain level the arterial blood pressure likewise rises and that it tends to maintain itself above the level of intracranial pressure. It appears likely that one reason why hypertension not uncommonly develops in a patient in the later stages of congestive heart failure is that there is increased intracranial pressure brought on by the increased venous pressure of cardiac failure.

SUMMARY AND CONCLUSIONS

1. The cerebrospinal fluid pressure is markedly elevated in persons with congestive heart failure.

2. The cerebrospinal fluid pressure, except for slight variations, usually runs closely parallel to the venous pressure in the prone position in persons with cardiac failure and, as a rule, the average ratio between the spinal fluid pressure and the venous pressure (1.6) in the patient with cardiac disease corresponds closely to that in the normal person. In general, either may be predicted from knowing the other.

14. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension, Am. J. M. Sc. **124**:375, 1902; The Blood Pressure Reaction of Acute Cerebral Compression Illustrated by Cases of Intracranial Hemorrhage, Am. J. M. Sc. **125**:1017, 1903.

3. The fall in cerebrospinal fluid pressure usually runs closely parallel with the fall in venous pressure as the patient with cardiac failure regains compensation.

4. Spinal drainage in patients with congestive heart failure was followed by a fall in venous pressure in eight instances, by a rise in two instances and by no change in three instances. In the majority of cases spinal drainage was followed by a decrease in dyspnea.

5. The cisternal pressure is much less in patients in the sitting than in the prone position, although the systemic venous pressure and spinal fluid pressure are greater. This difference in cisternal pressure and hence in cerebral venous pressure is more pronounced in patients with cardiac failure; its bearing on orthopnea is discussed.

6. The relationship of the increased intracranial pressure to Cheyne-Stokes' respiration and hypertension in patients with congestive heart failure is discussed.

HEREDITY IN ARTERIOLAR (ESSENTIAL) HYPERTENSION

A CLINICAL STUDY OF THE BLOOD PRESSURE OF 1,524 MEMBERS OF 277 FAMILIES

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Heredity is the most important known factor in the development of arteriolar (essential) hypertension. Valuable evidence for this opinion can be secured by studying the blood pressure in a large number of hypertensive and nonhypertensive families, with an effort to obtain the blood pressure readings of all of the available relatives in two or more generations. This has been the purpose and method of the present study.

REVIEW OF THE LITERATURE

A definite relationship between heredity and arteriolar (essential) hypertension and its complications was noted long ago by Dieulafoy, Raymond, Broadbent, Gowers, Allbutt [1] and others. More recently, this relationship was further demonstrated by the results of systematic studies of family histories. In the studies, O'Hare, Walker and Vickers [2] and Weitz [3] showed that a history of cardiovascular disease is frequent among the relatives of hypertensive patients. Weitz [3] showed in addition that there was an abnormally high incidence of elevated blood pressure readings among the brothers and sisters of his hypertensive patients as compared with the frequency of elevated readings in the brothers and sisters of people with normal blood pressure.

Other evidence showing the close relationship between heredity and arteriolar hypertension consists of several reports of families in which the disease was prevalent. De Nador-Nikititch [4] reported a family in

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From the medical service of the Beth Israel Hospital and the Boston Dispensary.

1. Dieulafoy, M.: Du rôle de l'hérédité dans la production de l'hémorrhagie cérébrale, Gaz. hebd. de méd. **13**:594 (Sept. 22) 1876. Raymond, P.: L'hérédité dans l'hémorrhagie cérébrale, Progrès méd. **23**:196 (March 30) 1907. Broadbent, W. H.: Heart Disease, New York, William Wood & Company, 1898, p. 80. Gowers, W. R.: Diseases of the Nervous System, London, J. & A. Churchill, 1893, vol. 2, p. 386. Allbutt, C.: Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915, vol. 1, pp. 164 and 412.

2. O'Hare, J. P.; Walker, W. G., and Vickers, M. C.: Heredity and Hypertension, J. A. M. A. **83**:27 (July 5) 1924.

3. Weitz, W.: Zur Aetiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med. **96**:151, 1923.

4. de Nador-Nikititch, Etienne: Sur l'étiologie de l'hypertension artérielle essentielle, Arch. d. mal. du cœur **18**:582 (Sept.) 1925.

which he found hypertension in the one parent studied and in 5 of 8 children. He presented only one reading of the blood pressure in each person. Rosenbloom [5] reported a family consisting of the parents and 10 children. He stated that 8 of the 10 children had arteriolar hypertension. The readings of the blood pressure were reported in only 4 of the 8 children. He also stated that the parents died of cerebral hemorrhage, but he did not present their blood pressure readings. Dawson [6] described 2 families containing 3 and 5 members, respectively. In both of the families, representing two generations, elevated readings of the blood pressure were found in all of the members. Weitz [7] reported 7 families, and Badía Brandia [8] described 4, in all of which, by a combination of family history and blood pressure readings, they considered arteriolar hypertension present in at least one member of each of two or three generations. I [9] recently reported a family in which I studied the blood pressure of every member for three generations, totaling 32 members above 13 years of age. It was found that 100 per cent of the first generation, 80 per cent of the second generation and 25 per cent of the third generation had elevated readings of the blood pressure on two or more visits. This apparently is the first family reported in which by direct study of the blood pressure elevated readings were found in three generations.

METHODS AND MATERIAL

Method.—It was decided that the most efficient way of examining the relatives of patients was to meet them when they came to the hospital to visit the patients. This method did not always permit the study of as many relatives of an individual family as did the earlier method of going to the homes, but it allowed the study of a much larger number of families and individuals. As a rule, the original patient in the hospital would explain the study to some of his relatives, who in turn would explain it to the others, so that when the relatives arrived, they knew what was to be done. On arrival at the hospital, the relatives were allowed to go to the patient's bedside and to rest and talk for a minimum of five minutes. The purpose of the study was then carefully explained to each relative so as to allay excitement as much as possible. Then, with the relative sitting in a chair and his arm resting on the patient's bed, the blood pressure was taken and a rough

5. Rosenbloom, J.: Familial Hypertension with Report of a Case, J. Lab. & Clin. Med. **8**:681 (July) 1923.

6. Dawson: Hyperpiesis, Brit. M. J. **2**:1161 (Dec. 19) 1925.

7. Weitz, W.: Ueber die Bedeutung der Erbmasse für die Aetiologie der Herz- und Gefässkrankheiten, Sonderabdruck über Hypertension (Aerztlicher Fortbildungskurs in Bad Nauheim, Pfingsten, 1926).

8. Badía Brandia, M.: El factor herencia en la etiología de la hipertonía esencial, Rev. méd. de Barcelona **13**:3 (Jan.) 1930.

9. Ayman, D.: The Hereditary Aspect of Arteriolar (Essential) Hypertension, Report of a Family, New England J. Med. **209**:194 (July 27) 1933.

estimation of the pulse rate was noted. Next, the person was asked his age, height and weight. The majority of the people knew their weight fairly accurately, and many of them knew their height. In cases in which the height was unknown, the subject was asked to stand, and his height was roughly gaged. The determination of the blood pressure was then repeated. In many cases, when the blood pressure readings were elevated, it was possible to check them on later visits. I made all of the readings, using a mercury sphygmomanometer. The end of the third (auscultatory) phase was taken as the criterion of diastolic blood pressure.

Material.—The blood pressure of 1,770 members of 345 hypertensive and nonhypertensive families was studied. The families of successive patients admitted to the surgical and medical wards of the Beth Israel Hospital were utilized without selection. However, in tabulating the results, many of the families had to be omitted because of inadequate data. Thus it was necessary to omit families in which only one parent was available, if this parent had a normal blood pressure, for the unavailable parent might have arteriolar hypertension. However, families were utilized in which arteriolar hypertension was found in the only parent available. Families were omitted in which both parents had normal blood pressure readings, if one of the parents was seriously ill, cachectic or markedly anemic, for such persons may have had a previous hypertension. Families in which one of the parents had nephritis or one of the parents stated that his blood pressure had been elevated in the past but at the time of the examination was normal were also omitted. These omissions reduced the total number of people included in the accompanying analysis to 1,524 and the total number of families to 277.

Method of Analyzing Results.—The families studied were grouped according to the presence or absence of arteriolar hypertension in one or both parents. In table 1, it is seen that the normal division (groups 1, 2, 3 and 4) consists of families in which both parents had blood pressure readings within the limits of normal.[10] This normal division was divided into four groups on the basis of the age of the parents and the height of their normal blood pressures. Thus, groups 1 and 2 consist of families in which both parents were 50 years or more of age, but in group 1 both parents had blood pressure readings of less than 138 systolic and 90 diastolic, whereas in group 2 at least one of the parents had a blood pressure reading of from 140 to 150 systolic and of less than 90 diastolic. Groups 3 and 4 consist of families in which the mothers were 49 years of age or less, the blood pressure in group 3 being 136 or less systolic and 90 or less diastolic; in group 4, from 136 to 150 systolic and 90 or less diastolic. It should be noted that in group 4, in which the blood pressure is a high normal and the mothers are 49 years of age or less, some of these parents may develop arteriolar hypertension later. It should also be noted that, in this normal division, the blood pressure figures given in table 1 indicate the highest reading obtained for the parents, despite the fact that most of the parents had lower readings at the first or subsequent determination.

The intermediate division, groups 5, 6, 7 and 8, consists of families in which elevated blood pressure readings occurred in at least one of the parents on the first determination, but in which the readings were either normal or much lower on subsequent visits or were not repeated at all. The individual groups within this division have been based chiefly on the height of the blood pressure in the parents.

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10. Rogers, O. H., and Hunter, A. W.: Mortality Study of Impaired Lives, Proc. A. Life Insur. M. Dir. America **10**:43, 1923.

The definitely hypertensive division (groups 9, 10, 11 and 12) consists of families in which one or both parents had undoubted arteriolar hypertension on at least two visits and usually on many occasions. In these parents the blood pressure readings were all above 160 systolic and 90 diastolic. Thus, group 9 was composed of families in which one parent had arteriolar hypertension and the other parent either normal or questionably normal blood pressure. Group 10 consists of families in which one parent had arteriolar hypertension, while the other was not available

TABLE 1.—*Analysis of 1,524 Patients and 277 Families Reported in This Study*

Division	Family Group	No. of Parents Examined in Family	Age of Parents	Blood Pressure of Parents		No. of Families	Total No. of Parents	No. of Children Aged 14 to 39, Inclusive	No. of Male Children Aged 14 to 39, Inclusive	No. of Children Aged 40 or Over	No. of Brothers and Sisters of Parents
				Systolic	Diastolic						
Normal	1	2	51 or more	138 or less	Below 90	10	20	32	11	2	..
	2	2	50 or more	140 to 150	Below 90	15	30	52	25	0	..
	3	2	Females, 49 or less	136 or less	Below 90	35	70	77	37	0	..
	4	2	Females, 49 or less	136 to 150	90 or less	19	38	49	23	0	..
Intermediate	5	2	50 or more	150 to 170	100 or less	28	56	78	31	21	..
	6	2	Females, 49 or less	140 to 170	100 or less	19	38	46	19	0	..
	7	2	50 or more	170 to 190	100 or less	40	72	121	53	19	..
	8	2	50 or more	200 or more	118 or less	16	26	23	9	16	..
Hypertensive	9	2	All ages	.....	Other parent normal	50	100	166	87	9	..
	10	1	50 or more	Essential hypertension* in one parent	Other parent unavailable	23	23	59	33	7	..
	11	1	58 or more	.....	Other parent unavailable but has history of hypertension	8	8	32	15	5	..
	12	2	Chiefly over 50	Both parents have hypertension*		14	28	55	32	2	..
Total (1,524)						277	489	780	375	79	176

* Over 160 systolic and 90 diastolic on two or more visits.

for examination and was not known to have an elevated blood pressure or cardiovascular disease. Group 11 was made up of families in which one parent had arteriolar hypertension, while the other parent, though not available for examination, was known either to be suffering from, or to have died of, arteriolar hypertension and its complications. Group 12 was composed of families in which both parents had arteriolar hypertension.

Finally, group 13, not presented in table 1, consisted of both normal and hypertensive families in which three generations were available for study.

The age, blood pressure, number of parents and number and sex of the children studied in each group are also presented in table 1.

TABLE 2.—*Systolic Blood Pressure Readings of the 780 Children, Aged from 14 to 39, Inclusive, Arranged by Percentage Incidence in Each Family Group*

	Groups											
Systolic Blood Pressure	Normal Parent(s)				Intermediate				Hypertensive Parent(s)			
	1	2	3	4	5	6	7	8	9	10	11	12
85- 89	....	....	1.3	....	....	....	....	....	....	....	....	....
90- 94	3.2	1.9	3.9	....	....	....	0.9	....	0.6	1.7	....	....
95- 99	9.7	1.9	1.3	1.8	2.9	....	0.9	....	0.6	....	....	....
100-104	16.0	9.3	9.1	5.6	5.7	4.3	3.5	4.4	4.8	3.4	....	1.9
105-109	6.4	7.4	6.5	....	7.2	2.2	3.5	4.4	3.6	1.7	....	1.9
110-114	19.3	20.4	18.2	10.8	10.0	12.9	11.0	17.6	12.6	11.9	12.5	....
115-119	9.7	9.3	6.5	18.0	7.2	12.9	9.6	4.4	6.0	5.1	12.5	1.9
120-124	19.3	20.4	18.2	16.2	25.7	11.0	20.0	26.4	12.6	11.9	6.3	9.3
125-129	3.2	1.9	3.9	16.2	8.6	17.2	7.0	4.4	6.6	11.9	9.4	5.6
130-134	6.4	11.1	13.0	16.2	18.6	11.0	11.2	13.2	15.0	10.2	21.9	13.0
135-139	3.2	7.4	3.9	1.8	1.4	6.6	6.1	....	5.4	5.1	6.3	9.3
140-144	3.2	3.8	9.1	5.6	10.0	8.8	14.8	22.0	16.8	8.5	9.4	20.4
145-149	....	1.9	....	....	....	4.4	3.5	....	3.6	3.4	9.4	5.6
150-154	....	1.9	2.6	....	....	8.8	2.7	....	7.2	10.2	6.3	14.8
155-159	....	1.9	....	....	2.9	4.3	0.9	....	0.6	5.1	....	5.6
160-164	....	....	1.3	....	....	2.2	1.8	....	2.4	5.1	6.3	3.7
165-169	....	....	....	....	....	....	....	....	....	1.7	....	....
170-174	....	....	....	....	....	....	....	....	1.8	....	....	3.7
175-179	....	....	....	....	....	....	....	....	....	....	....	....
180-184	....	....	....	....	....	....	....	....	0.6	1.7	....	....
185-189	....	....	....	....	....	....	....	....	....	....	....	1.9
190-194	....	....	....	....	....	....	0.9	....	....	....	....	....
195-199	....	....	....	....	....	....	....	....	....	....	....	....
200-204	....	....	....	....	....	....	....	....	....	1.7	....	1.9
Percentage Incidence												
Above 139 mm. Hg	3.2	9.5	13.0	5.6	12.9	28.5	24.6	22.0	32.8	37.4	31.4	57.6
144 mm. Hg	0.0	5.7	3.9	0.0	2.9	19.7	9.8	0.0	16.0	28.9	22.0	31.6
Below 105 mm. Hg	28.9	13.1	15.6	7.4	8.6	4.3	5.3	4.4	6.0	5.1	0.0	1.9

TABLE 3.—*Diastolic Blood Pressure Readings of the 780 Children Aged from 14 to 39, Inclusive, Arranged by Percentage Incidence in Each Group*

	Groups											
Diastolic Blood Pressure	Normal Parent(s)				Intermediate				Hypertensive Parent(s)			
	1	2	3	4	5	6	7	8	9	10	11	12
40- 49	....	....	....	....	3.2	....	....	....	....	....	....	....
50- 54	15.5	3.8	1.4	....	....	....	2.7	....	1.8	....	....	....
55- 59	3.1	3.8	2.7	3.8	3.2	2.2	0.9	4.4	1.2	1.7	....	....
60- 64	15.5	13.4	15.2	7.7	6.4	4.3	6.3	17.6	12.0	10.2	....	1.9
65- 69	6.2	23.0	17.5	5.8	7.8	11.0	6.3	13.2	6.0	1.7	6.6	3.7
70- 74	37.2	32.6	20.8	19.2	26.5	24.2	27.9	17.6	21.6	18.7	9.9	13.0
75- 79	9.3	7.7	12.5	17.3	7.8	15.4	13.5	17.6	9.6	18.7	16.5	16.7
80- 84	6.2	21.1	22.2	23.0	21.8	8.8	23.0	22.0	18.0	24.8	23.1	29.6
85- 89	3.1	1.9	5.5	5.8	15.6	8.8	8.1	8.8	11.4	10.2	26.4	3.7
90- 94	....	7.7	5.5	5.8	7.8	6.6	9.0	....	14.5	11.9	13.2	16.7
95- 99	3.1	1.9	....	....	....	6.6	0.9	....	1.8	....	....	9.3
100-104	....	1.9	....	....	1.6	2.2	0.9	....	1.8	1.7	3.3	3.7
105-109	....	....	....	....	....	2.2	....	....	....	....	....	....
110-114	....	....	....	....	....	....	0.9	....	....	....	....	....
115-119	....	....	....	....	....	....	....	....	....	....	....	....
120-124	....	....	....	....	....	....	....	....	....	1.7	....	1.9
125-129	....	....	....	....	....	....	....	....	....	....	....	....
130-134	....	....	....	....	....	....	0.9	....	....	....	....	....
135-139	....	....	....	....	....	....	....	....	....	....	....	....
140-144	....	....	....	....	....	....	0.9	....	....	....	....	....
Percentage Incidence												
Above 84 mm. Hg	6.2	13.4	11.0	11.6	25.0	26.4	21.6	8.8	29.5	25.5	42.9	35.3
Below 60 mm. Hg	18.6	7.6	4.1	3.8	6.4	2.2	3.6	4.4	3.0	1.7	0.0	0.0

BLOOD PRESSURE READINGS IN CHILDREN

Analysis by Family Groups of All the Blood Pressure Readings.—In tables 2 and 3 are presented the systolic and diastolic blood pressure readings of the children arranged according to family groups. They were the highest systolic and diastolic readings found for the individual person on the first visit. The figures in the tables indicate the percentage incidence of the blood pressure readings for each rise of 5 mm. of mercury in systolic and diastolic blood pressure. In these tables it is seen that above a systolic level of 139 mm. or a diastolic level of 84 mm. there was a markedly higher incidence of blood pressure readings in the children of the hypertensive division than in those of the normal groups. For example, table 2 shows that the incidence of systolic blood pressure readings above 139 mm. rose from 3.2 per cent for the strictly normal persons (group 1) to 57.6 per cent for the hypertensive persons (group 12). If one averages the incidence for each division of four groups, it is found that 7.9 per cent of the children of the normal division, 21.8 per cent of the intermediate division and 39.8 per cent of the hypertensive division had systolic blood pressure readings above 139 mm. If one determines the percentage of systolic readings above 144 mm., the differences are even more striking, showing 2.4 per cent for the normal, 8.1 per cent for the intermediate and 24.6 per cent for the hypertensive division. Similarly, if one takes a dividing level of 84 mm. for the diastolic blood pressure, it is found that in the normal division (groups 1, 2, 3 and 4) 10.6 per cent of the readings were above 84 mm.; in the intermediate division, 20.5 per cent, and in the hypertensive division, 33.3 per cent (table 3).

In contrast, the incidence of systolic readings below 105 mm. and diastolic readings below 60 mm. was much higher in the normal division than in the hypertensive division. The tables do not indicate how often elevated systolic and diastolic readings occurred together in the various groups.

Incidence of Simultaneously Elevated Systolic and Diastolic Readings.—The occurrence of both an elevated systolic and an elevated diastolic blood pressure in the same person is probably more important than the occurrence of either an elevated systolic or an elevated diastolic blood pressure alone. In this part of the analysis, a blood pressure of 140 systolic, and 80 diastolic, or higher, was considered above normal for persons between the ages of 14 and 39.[10] In reality, most of the people to be discussed in this section had blood pressure readings well above 140 systolic and 80 diastolic. Referring to table 4, it is seen that the incidence of elevated blood pressure readings in the children, as determined for each group of parents, shows a striking increase as one goes from the groups with normal parents to those with hypertensive parents. Thus, in group 1, which was composed of families in which both parents

had absolutely normal blood pressure readings and were over 50 years of age, the incidence of elevated blood pressure readings in the children was only 3.1 per cent; that is, only 1 of the 31 children in this group. Turning to the other group of extreme cases, group 12, in which both parents had undoubted arteriolar hypertension, one finds a striking incidence of elevated readings in the children, amounting to 45.4 per cent, that is, 25 of 55 persons. A similar striking difference is seen on comparing the incidence in each division of family groups, the incidence of elevated readings in the normal division (groups 1, 2, 3 and 4) being 5.5 per cent; in the intermediate division, 17.1 per cent, and in the hypertensive division, 31.9 per cent. It is to be noted that in group 5, composed of parents who were over 50 years of age, at least one of

TABLE 4.—*Incidence in 780 Children of Elevated Blood Pressure Readings of 140 Systolic and 80 or More Diastolic*

Family Group	Children Studied, Aged 14-39, Total Number	Children with Blood Pressure 140/80 or More	
		Number	Percentage of Total
1	32	1	3.1
2	52	3	5.8
3	77	4	5.2
4	49	4	8.2
Total	210	12	Average 5.5
5	78	6	7.7
6	46	9	19.5
7	121	18	14.9
8	23	6	26.0
Total	268	39	Average 17.1
9	166	47	28.3
10	59	17	28.8
11	32	8	25.0
12	55	25	45.4
Total	312	97	Average 31.9

whom showed on the first visit blood pressure readings of from 150 to 170 systolic and of 100 or less diastolic, the incidence of elevated readings in the children was only 7.7 per cent.

Analysis of the Group of Children with Elevated Blood Pressure Readings (140 Systolic and 80 or More Diastolic).—As seen in table 4, there were 148 children with blood pressure readings of 140 systolic and 80 diastolic, or higher. In reality, 75 of the 148 children had systolic blood pressures of 150 or more, and 30 of the 148 had systolic readings of 160 or more. In 84 of the 148 children, the diastolic blood pressure was 90 mm. or more; in 27 it was 96 mm. or more, and in 17 it was 100 mm. or more. Blood pressure readings had been made before by other physicians in 118 of the 148 children, and 19 of these 118 knew that their blood pressure was elevated at the time. Sixty-two of the 148 were seen by me on a second visit, and at this time 40 of the 62 still

showed elevated blood pressure readings. In 18 of the 148, it was noted that a rapid pulse was present while the blood pressure was being taken.

The weight of the children with elevated blood pressure readings as compared with the weight of the children with normal blood pressure readings is presented in table 5. All of the normal children whose weights are presented in table 5 had blood pressures of 130 systolic and 84 diastolic, or less. It is seen that in the hypertensive division, 97 children with elevated readings had an average weight of 13⅕ pounds (6 Kg.) above the normal for their sex, age, and height,[11] while 115

TABLE 5.—*The Average Weight of "Hypertensive" Children as Compared with Normal Children*

	"Hypertensive" Children		Normal Children	
Family Division	Number	Pounds Above Normal	Number	Pounds Above Normal
Normal	12	+ 8.1	154	+4.2
Intermediate	39	+14.2	...	.....
Hypertensive	97	+13.2	115	+4.8
Total	148		269	
Average		+14.3		+4.5

TABLE 6.—*Average Age of "Hypertensive" Children, as Compared with All of the Children*

Family Groups	Average Age of All Children, Years		Average Age of Hypertensive Children, Years	
1	25.5			
2	26.3	23.0		22.1
3	20.2			
4	19.9			
5	26.5		25.8	
6	20.9	26.2	20.0	26.5
7	27.8		29.4	
8	29.5		30.6	
9	26.0		28.2	
11	25.9	26.8	26.5	28.7
11	28.8		32.3	
12	26.4		27.8	

normal children in the hypertensive division were only 4⅘ pounds (2.1 Kg.) above normal. The average weight for the 148 children with elevated readings was 14⅗ pounds (6.48 Kg.) above the normal, and for 269 normal children it was 4½ pounds (2 Kg.) above the normal.

Table 6 shows that the average age of the children with elevated readings in each group was strikingly similar to that of all of the children in the groups.

11. Metropolitan Life Insurance Company, Study of the Weight of 200,000 Insured Individuals.

The incidence of elevated blood pressure readings by sex is seen in table 7. In this table it is first to be noted that there was a fairly equal distribution of the sexes among the 780 children studied. On the other hand, the comparatively small number of children with elevated readings made their average of little significance. In general, there was, roughly, as high an incidence of elevated readings in the males as in the females, though it was perhaps slightly higher in the males. Thus, of 148 patients with elevated readings, 91 (61.5 per cent) were males.

Questionably Elevated Blood Pressures.—There were 47 children who had either an elevated systolic reading or an elevated diastolic reading, but not both. The group with elevated systolic readings alone had systolic readings of 140 or higher, and diastolic readings below 80 mm. There were 28 such persons, in 24 of whom the systolic read-

TABLE 7.—*Sex Incidence in the Normal Children as Compared with that in Children Having Elevated Blood Pressure Readings*

Family Group	Males in the 780 Children, per Cent		Males in the 148 Hypertensive Children, per Cent	
1	46	44.7	0	45.8
2	51		66.6	
3	48		66.6	
4	34		50.0	
5	46	45.0	33.3	51.3
6	50		66.6	
7	45		72.0	
8	39		33.3	
9	51.7	53.2	72.0	62.0
10	52.2		41.0	
11	50.0		75.0	
12	59.0		60.0	

ings were between 140 and 144, and in the remaining 4 from 145 to 156. In 27 of the 28 children, the diastolic readings were between 70 and 78 mm. Whenever a high pulse pressure was encountered in the children, auscultation of the heart was practiced, and in this way 3 cases of aortic regurgitation were discovered; they were omitted from the figures. There were 19 children whose diastolic readings were between 90 and 94 mm. and whose systolic readings were between 130 and 138. In general, the children with either elevated systolic or elevated diastolic readings occurred in the same frequency in the normal, intermediate and hypertensive divisions.

BLOOD PRESSURE READINGS OF THE BROTHERS AND SISTERS OF THE PARENTS

It was possible to study the blood pressure of 176 brothers and sisters of the children's parents. Twenty of the 176 had questionably elevated blood pressure readings and were not included in the results. Of the remaining 156 (table 8), 70 were brothers and sisters of the

parents with normal blood pressure, and 86 were brothers and sisters of the parents with arteriolar hypertension. As seen in table 8, 37.3 per cent of the brothers and sisters of the normal parents had definitely elevated blood pressures as compared with the normal standards,[10] whereas 65.3 per cent of the brothers and sisters of the hypertensive parents had elevated readings.

FAMILIES IN WHICH THREE GENERATIONS WERE STUDIED

There were 18 families in each of which three generations were studied. The individual parts of each of these families, consisting of one or more parents with children, have already been included in the family groups already analyzed. It was not possible to study all the members of the three generations, as in the detailed study of the family of three generations recently reported by me.[9] It was possible, however, to study 185 members of the 18 families. In 16 of the 18 families, there was

TABLE 8.—*Incidence of Elevated Blood Pressure Readings in the Brothers and Sisters of the Parents*

	Number with Normal Blood Pressure	Number and per Cent with Elevated Blood Pressure
Brother and sisters of parents with normal blood pressure	51	19 (37.3%)
Brothers and sisters of parents with arteriolar hypertension	32	54 (65.3%)

definite arteriolar hypertension in one or both grandparents studied, that is, the first generation. The second generations of these 16 families were composed of 59 persons, 30 of whom had definitely elevated systolic and diastolic blood pressure readings. In the third or youngest generations that were studied, there were 37 persons, 8 of whom had elevated systolic and diastolic readings. Of the two families in which the grandparents (first generation) had normal blood pressure, all 7 members of the second generations had normal blood pressure. Although the entire present study is based on actual blood pressure readings, it is interesting to note that in 3 of these families of three generations, the family history in the great-grandparents or fourth generation was positive for cardiovascular disease.

Although no systematic analysis of the personalities or body-build of these persons was made, it was noted that a large number of the hypertensive children in the present investigation were of the highstrung hyperactive type described in a previous investigation of hypertensive persons.[12] They usually resembled their hypertensive parent in this respect. In addition, like their hypertensive parent, they were most often of the sthenic type.

12. Ayman, D.: The Personality Type of Patients with Arteriolar (Essential) Hypertension, Am. J. M. Sc. **186**:213 (Aug.) 1933.

SUMMARY

To determine more clearly the presence of a familial or hereditary factor in arteriolar (essential) hypertension, a direct study of the blood pressure, height and weight of 1,524 members of 277 families was made.

It was found that in 780 members, aged from 14 to 39 years, of the second generation of the families, elevated systolic and diastolic blood pressure readings (140 systolic and 80 diastolic, or higher) occurred in 148 subjects. These 148 subjects had the same average age and sex incidence as the entire group of 780 children, but they were $14\frac{3}{10}$ pounds above the average weight compared to $4\frac{1}{2}$ pounds above the average weight for the normal children.

The families studied were then grouped according to the presence or absence of arteriolar (essential) hypertension in one or both parents. In the families whose parents had absolutely normal blood pressures, the incidence of elevated blood pressures in the children was only 3.1 per cent. In the families in which one parent had arteriolar hypertension, the incidence of elevated readings in the children rose to 28.3 per cent. In the families in which both parents had arteriolar hypertension the incidence of elevated readings in the children reached the striking level of 45.5 per cent.

Of 70 brothers and sisters of parents with normal blood pressures, 37.3 per cent had elevated blood pressure readings, whereas of 86 brothers and sisters of parents with arteriolar hypertension, 65.3 per cent had elevated blood pressure readings.

Finally, I studied 18 families in which parts of three generations were available and found the results strikingly similar to those given in the preceding paragraph.

The results presented show that there is an unusually high incidence of elevated blood pressure readings in the children, brothers, sisters and parents of subjects with arteriolar hypertension, as compared with similar relatives of subjects with normal blood pressure. These results are strong evidence for the existence of a hereditary factor in arteriolar (essential) hypertension.

371 Commonwealth Avenue.

News and Comment

EDWARD M. GIBBS MEMORIAL PRIZE

It is announced by the New York Academy of Medicine, 2 East One Hundred and Third Street, that a sum of approximately $800 is available under the Edward M. Gibbs Memorial Prize toward original research in diseases of the kidney during 1934. Candidates, who must be physicians who have been graduated at least three years and residents of the United States, shall submit "Evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney." The award may be continued through not more than three years to any one person. Applications with the required evidence should be addressed to the New York Academy of Medicine prior to June 1.

MEETING OF AMERICAN HEART ASSOCIATION

The Tenth Scientific Session of the American Heart Association will be held on Tuesday, June 12, 1934, at the Cleveland Hotel, Cleveland. The program will be devoted to arteriosclerotic heart disease.

Book Reviews

Handbuch der allgemeinen Hämatologie. Edited by Hans Hirschfeld and Anton Hittmair. Volume II, part 1. Price, 55 marks. Pp. 700, with 259 text figures and 4 colored plates. Berlin: Urban & Schwarzenberg, 1933.

Volume I of this handbook has already been reviewed (ARCH. INT. MED. **52**:821 [Nov.] 1933). Volume II, part 1, deals with the technic of examination of the blood. Part 2, which remains to be published, will be devoted to a consideration of the blood plasma.

The technic of examination of the blood is covered in a series of twenty-three monographs, two of which have been written by Hirschfeld, the senior editor, and nine by Hittmair, while the remaining chapters are supplied by eight German contributors and one Danish contributor.

In the first chapter (Hittmair, pages 1 to 16), elementary information concerning methods of obtaining blood is presented in considerable detail. The description of methods of collecting blood from various animals will be found useful. Surprisingly brief attention is given to the examination of fresh blood (Hittmair, pages 17 to 19), and its importance in the demonstration of sickling is not even mentioned. In the third chapter (Hittmair, dark-field examination, pages 21 to 28), ultramicroscopy is briefly discussed.

Under the title "Theory of Staining" (pages 29 to 94) Mommsen has written a detailed monograph on the chemical and physicochemical aspects of the staining of blood. In the following chapter (pages 95 to 118) Hirschfeld and Moldawsky discuss at length the staining and significance of reticulocytes and devote several pages as well as three colored plates to the supravital staining of leukocytes with azure II. Sabin's method, however, is dismissed with half a page of technical description and the statement that "the method is no longer recognized as an accurate means of differentiating between monocytes and other mononuclear forms and has been rejected, among others, by Naegeli." Even those who have not subscribed to the enthusiasm exhibited by Sabin's followers must be surprised at this cursory treatment of her work.

The measurement of the size (actually, diameter) of the formed elements of the blood (Hittmair, pages 119 to 124) is given attention so brief as to be out of proportion to the unrestricted length of most of the chapters in this handbook. The Price-Jones method, which is at least of historical interest, has been ignored.

A chapter on the staining of dry preparations (Hittmair, pages 125 to 168) and the special section on the demonstration of the intracellular ferments of leukocytes (Hirschfeld, pages 169 to 175) are replete with details and bring together useful information concerning a great variety of special stains. The discussion of the methods and technic of cytodiagnosis (Zadek, pages 177 to 196) supplements the excellent monograph on transudates and exudates by the same author in volume I. In the succeeding chapter (pages 197 to 228), methods of obtaining, fixing, decalcifying, mounting and staining bone marrow are ably reviewed by Petri, and a variety of special stains is described.

Hittmair discusses methods of hemoglobin determination and cell counting at great length (pages 239 to 318). The lack of a satisfactory method for hemoglobin determination is well illustrated by the number of instruments devised for this purpose. Hittmair has found it impossible to include them all within thirty-six pages. Methods of blood counting and a great variety of hemacytometers are described in detail. Yet nothing is said about the historical development of blood counting, and one notes the omission of mention of the Bass-Johns chamber and such a generally used diluent for platelet counting as Rees and Ecker's solution. A great variety of hemoglobin indexes is recapitulated, but, in the opinion of the reviewer, this simply makes confusion. One would welcome some critical evaluation by the author.

An excellent critical discussion of hematocrit methods is presented in the chapter on the determination of red cell volume (Heilmeyer, pages 345 to 372),

and a great variety of indirect methods is described and critically evaluated. The chapter on the technic of blood sedimentation (Leffkowitz, pages 435 to 490) is perhaps the best available review of the subject and leaves no room for criticism. The section devoted to the fragility of the red corpuscles (Simmel, pages 495 to 584) is detailed and offers considerable information for the clinical hematologist. The latter will also find the chapter on blood coagulation (Schultz, pages 645 to 700) of value, particularly on account of the description of infrequently used methods, many of which are unknown in this country.

Chapters on the determination of the specific gravity (pages 329 to 344) and the viscosity (pages 373 to 406) of blood and on refractometry (pages 407 to 434), all by Heilmeyer, include considerations of physical principles, methods, normal values and influencing factors. Schumm contributes a section on the spectroscopic and spectrographic examination of blood (pages 585 to 618).

Mertens discusses in detail the qualitative and quantitative determination of bilirubin (pages 619 to 644). Short sections are devoted to the guttadiaphot (Hittmair, pages 491 to 494), the photography and drawing of microscopic preparations (Hittmair, pages 229 to 238) and the methods of calculating error and probability in hematologic technic (Hittmair, pages 319 to 328).

The writers of this treatise have succeeded in bringing together a wealth of information which previously was scattered in such a variety of journals as to be accessible only through much loss of time. Extensive bibliographies make this an important reference work. Unfortunately, emphasis is given to the German literature, and American contributions are somewhat inadequately considered. In several chapters the discussion is so elementary and verbose as to detract seriously from the usefulness of the information. A critical evaluation of methods, which the writers' experience should have permitted them to make, is frequently sought for in vain. Although the typography is good, a more liberal use of heavy type would have facilitated the quick selection of information. In comparison with the usefulness of this handbook, these objections are not, however, of great importance. Both the teacher and the investigator will find this book invaluable.

Pediatrics. By Henry Dwight Chapin and Lawrence T. Royster. Seventh edition, revised and rewritten by Lawrence T. Royster. Price, $7. Pp. 775. Baltimore: William Wood & Company, 1933.

The ideal textbook of pediatrics is one which confines itself to those conditions peculiar to childhood and to the special manifestations of disease in children. Adequate and for that matter outstanding texts of general medicine are always readily available; to duplicate in treatises on pediatrics discussions of infectious disease, neurology and dermatology, except so far as the picture is significantly modified by the preadolescent state, seems ill advised and superfluous. Granted that practical considerations limit the size of ordinary textbooks to approximately 1,000 pages, then if matters of growth, development, infant feeding and special conditions of childhood are properly dealt with, insufficient space remains in which to do justice to general medicine, neurology and dermatology. The result is that what is said about typhoid fever, diabetes insipidus or multiple sclerosis may be too brief to be of use to one unfamiliar with the subject and yet too commonplace to interest or instruct those of even scant experience.

Whether or not the foregoing thesis is sound in principle, the fault of construction to which allusion has been made is evident in the present work. The chapters on growth and development, on the appraisal of the child, on injuries sustained at birth and diseases and abnormalities of the new-born, on the technic of examination, on infant feeding and on the care of premature infants are instructive and satisfying. This part of the treatise is clearly written with enthusiasm and *savior de metier*. The later sections, however, beginning with that on infectious disease, are disappointing; they consist of brief and inadequate summaries of what is better said in almost any current textbook of medicine. It is always easy for the reviewer to quarrel about minor points. One might

disagree, however, with the claim that the Bordet-Gengou bacillus is the specific organism of whooping cough in the face of the evidence recently brought forward by Rich and others in favor of an ultravirus. Even more disturbing is the view that influenza is most probably caused by "a mixed infection, with streptococcus predominating." That the authors are not soundly informed on current views of etiology of infectious disease is further borne out by their confused statements on erysipelas and acute tonsillitis, both now proved to be due to hemolytic streptococci. Fundamental concepts of tuberculous infection are dismissed with a few brief and inadequate paragraphs, and the evidence recently confirmed by Dochez that the common cold is caused by a filtrable virus appears to be unfamiliar to the writers. In the midst of the chapter on infectious disease one finds a heading "Rheumatoids" under which chronic arthritis is briefly discussed, and one is even more surprised in the section on ductless glands to encounter diseases of the spleen, Hodgkin's disease, acute and chronic adenitis and other irrelevant conditions. Diabetes insipidus, on the other hand, is discussed with disorders of the urine and kidneys. The sections on nephritis are wholly inadequate. "In attempting to classify the various forms of nephritis . . . the student at the bedside will be much confused." This confusion seems to exist equally in the minds of the writers, and certainly no remedy is brought out in the text.

On the whole, the reviewer believes that the subject could be treated in a more satisfactory manner; however, the writers' broad personal experience is evident, and the book will doubtless continue to be useful to those looking for clinical guidance in pediatrics.

Diabetes Mellitus. By I. M. Rabinowitch, M.D. With an introduction by A. M. MacCallum. Price, $3.50. Pp. 246. Toronto, Canada: The Macmillan Company of Canada, Ltd., 1933.

This book is written for the student in the medical school and for the practitioner. It covers in a concise way the principal features of diabetes with little reference to the physiology involved or other subjects of academic significance. In the matter of treatment stress is laid on the essentials; "the description of a method of treatment without a knowledge of blood sugar and alkali reserve, or the use of scales and without a detailed knowledge of the value of materials, is in the writer's opinion one of the chief justifications of the present publication."

The author has made use of an ingenious system of food models and standard measures to replace the unjustifiably expensive food scales. He has also abandoned the well known food tables in favor of lists of substitutions. His basic diet contains, in most cases, from ten to twelve average sized slices of bread, and the substitutions provide an equivalent amount of carbohydrate, including sweets, honey, jam and sugar. To enable the utilization of the high carbohydrate allowance without resort to prohibitive amounts of insulin, but mainly because it is supposed that a certain degree of undernutrition is desirable in diabetes, the total calories of the diet are restricted by rigid limitation of the allowance of fat. Limitation of fat is defended also on the supposititious ground that fat is injurious, a conclusion which is at best contentious. According to the text, "very few diabetics in the past had the disease for more than five years without the development of arteriosclerosis." The restriction of fat and calories which is imposed must detract considerably from the palatability of these diets, not to speak of the question of adequacy from the standpoint of meeting normal nutritional requirements.

The value of the book is considerably diminished by a somewhat dogmatic manner of presentation. An apology for this is offered, namely, that the author's experience in teaching has taught him "that if a handbook is to be useful it should contain that which the student can take with him on the date of graduation and make immediate use of." A wiser educational policy, in the mind of the reviewer, is one which encourages the critical attitude, particularly in the realm of therapy, where fashions change so frequently. The student might well be taught that methods of treatment which differ more or less radically may be used success-

fully by different physicians, and that methods successful in the hands of one may be less satisfactory when applied by another. This dictum seems to apply with special force to the treatment of diabetes.

Biochemistry of Medicine. By A. T. Cameron, Professor of Biochemistry, University of Manitoba, and C. R. Gilmour, Professor of Medicine, University of Manitoba. Price, $5.50. Pp. 506. New York: William Wood & Company, 1933.

Physicians and students of medicine receiving clinical instruction will find this book an invaluable aid in applying biochemistry to the practice of medicine. Approximately one fifth of the book is devoted to a summary of the present state of knowledge of the chemistry of carbohydrates, fats and proteins and of intermediary metabolism. The physician who has not kept up with the developments in biochemistry will find this book readable and worth reading. It has less value for the advanced student of medicine, since he has had a more comprehensive course. The remaining four fifths deals with the medical applications of biochemistry. The headings of some of the chapters are: "The Reduction Test for Urine and What It Connotes," "Non-Diabetic Glycosurias," "Diabetes Mellitus," "Abnormal Fat Metabolism," "The Albuminuria Test and What It Connotes," "Abnormal Metabolism of Proteins and Protein Derivatives," "Metabolism of Water" and "Liver Functions and Liver Functional Tests." The book contains a large amount of information which the physician needs. The authors have attempted to make the book readily usable by the physician. They have avoided controversial material, generally giving only the view which is most commonly accepted. Very little historical material is given. Sufficient references are given to assist the reader in finding significant articles in journals, but no attempt is made to give a complete bibliography. There is a brief summary at the end of most of the chapters. Research men looking for a comprehensive survey of the medical applications of biochemistry will look elsewhere.

The reviewer believes that the section on the chemistry of carbohydrates is not written as successfully as the remainder of the book. For example, the attempt to simplify the chemistry of dextrose by referring to it as a derivative of methyl alcohol and formaldehyde is unnecessary and confusing. Structural formulas could have been used more effectively than they were. The ring structure of dextrose which is now generally accepted is given in a footnote. Also, the reviewer believes that there is unnecessary repetition in the first one fifth of the book.

The book is a contribution to the medical literature, and physicians and students of medicine will find it an excellent aid in correlating biochemistry and medicine.

Les rythmes et la vie. By Laignel-Lavastine, A. M. Chanoz, J. Monchanin, G. Richard, J. Guitton, F. Mentré, H. Duprat, H. Cardot and R. Biot. (Groupe lyonnais d'études médicales, philosophiques et biologiques.) Paper. Price, 15 francs. Pp. 261. Lyon: Librairie Lavandier, 1933.

The introduction to this book explains that it is an effort on the part of its nine collaborating authors to synthesize the results of their work in diverse fields; these range from astronomy to subatomic physics. The result is rather more than popularized science; it is nearer philosophy in the Spencerian sense. Of the sections which have special medical interest, one in particular is likely to fascinate but irritate the medical reader. It is entitled "The Cosmic Influx and Human Life," and it summarizes the theory and assumed facts of astrology. General ignorance of the relations of physiology to meteorology makes it difficult to criticize the author's arguments in detail. The ancient vocabulary of quadratures, ascending nodes, conjunctions and oppositions at once prejudices the modern reader. But the author of this section, Duprat, does not alter his vocabulary to mollify his reader's prejudice; he rather provokes it further by citing details from the works of Maag, Krafft and others, and by suggesting that physicians may yet find it profitable to consider the phases of the moon before administering a drug.

Certainly there is an urgent need for more concrete and reliable information as to the effects of climate, season and weather on human beings in health and in disease. Although research of this kind is going on in this country, much more is needed, and much of it should be directed specifically to the questions raised by Duprat. The weakest part of the book is a section on nervous and endocrine rhythms. Here one finds, for instance, a statement that "it is easy to distinguish a physiogenic from a psychogenic anxiety state by the p_H of the urine." It is unnecessary to point out here how much harm can result from putting such controvertible statements into the popular literature. Taken as a whole, the book has a strong appeal as general reading.

Les hémorrhoïdes. By Jean Rachet, Physician to the Hospitals of Paris. Price, 25 francs. Pp. 80, with 16 illustrations. Paris: Gaston Doin & Cie, 1933.

This short monograph on the diagnosis and treatment of hemorrhoids is a fasciculation of a French system of practical medicine now appearing under the title of "La pratique médicale illustrée" and edited chiefly by Prof. E. Sergent of Paris. This particular article lives up to the title of the system and discusses hemorrhoids in a practical and interesting manner.

The author comments on the frequency of the disorder and on its inherent mildness. He describes how to examine the recto-anal region and the use of the anoscope, emphasizing how important it is for physicians to become familiar with such examinations and to recognize early malignant or possibly malignant lesions. He discusses treatment competently. He lays considerable stress on the general measures of hygiene which can be instituted to minimize the severity and occurrence of hemorrhoids. His local treatment is reasonable. He believes that sclerosing injections offer the best form of surgical treatment now available, and he describes the technic of such injections in detail. He is not especially enthusiastic regarding results obtained from the various electrical forms of therapy which have been devised, and advocates using but rarely more radical surgical procedures. On the whole, he has assembled a chapter on hemorrhoids which should prove an asset to the system of medicine for which it was written.

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